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A CONSIDERATION OF IMPROVED METHODS OF NEBULIZATION THERAPY

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INCREASING interest in the pathologic physiology of chronic bronchopulmonary disease has opened the way for more enthusiastic treatment of such conditions as chronic bronchitis, bronchiectasis, asthma and emphysema. Barach and his associates,[1,2] Segal and Dulfano[3] and Harvey, Ferrer and Cournand[4] have emphasized the reversibility of many of the severe states that characterize these disorders.

Nebulization and inhalation of various drugs is usually a very effective method of therapy when used properly in these diseases. On the other hand only transient or incomplete benefits result from nebulization therapy if the nebulizers are employed improperly.

The purpose of this report is to present an improved technic for use of the nebulizer, together with a discussion of certain nebulization medications and apparatus.

NEBULIZATION TECHNICS

Frequently, the custom has been to give patients a nebulizer and medication with instructions simply to take deep inhalations of a specified quantity of the medication. Careful observation during nebulization treatments of many patients with asthma and emphysema revealed that successive deep inhalations became progressively less effective. When the patients were attached to a spirometer and asked to repeat this type of inhalation a progressive decrease in inspiratory volume, with a progressive rise in respiratory midposition, resulted. The rising midposition represents air trapping (Fig. 1—inspiratory method). This method of nebulization (IM) provides a relatively rapid respiratory rate and small inspired volume in a large functional residual capacity, a situation that results in poor penetration and distribution of the nebulized medication.[5,6] Such breathing can further be expected to produce ineffective alveolar ventilation, so that in patients who are already hypoxic, while breathing room air, increased bronchospasm may even develop, owing to a fall in arterial oxygen tension.

A logical approach to the problem is the adoption of a nebulization technic that does not cause air trapping and provides a relatively large inspired volume at a slow respiratory rate. On this basis the expiratory-inspiratory-pause method shown in Figure 1 was instituted. According to this method (EIPM) the patient is asked to exhale fully, *but not forcibly.* It is important to emphasize that the exhalation should not be preceded by deep inspiration, which merely causes further air trapping. Inhalation of the nebulized material begins from the depth of the expiration. A slow, natural inspiration is taken, but no effort should be made to take a maximal inspiration. At the end of inspiration, the breath is held momentarily (for a second or two) to permit improved distribution and deposition of nebulized particles.

Careful studies on aerosol medication by Dautrebande[5] and Stalport[6] demonstrate the necessity for a slow respiratory rhythm with an inspiratory pause. With Stalport's data as a criterion, a maximum absorption of only 40 per cent of nebulized material by the simple inspiratory method, IM (Fig. 1), might be expected. On the other hand the expiratory-inspiratory-pause method (EIPM), as demonstrated in Figure 1, should result in at least 85 per cent absorption; this is a consequence of the fact that the procedure imposes on the patient a slow, effective respiratory rate with only modest respiratory effort. With this technic the patient takes six to ten inhalations per minute. The total number of inhalations depends on such factors as the type and dosage of drug being nebulized as well as the type of system being used to nebulize the medication. Hardly enough emphasis can be given to efforts to keep the treatment a slow, reasonably relaxed procedure with every attempt to avoid the stresses that would make it difficult for these frequently harassed patients. Since the EIPM facilitates rapid and effective penetration of the bronchodilating medication relief from bronchospasm is rapidly provided, thereby minimizing the tendency to continue nebulization to the point where systemic effects (cardiac and central) result from excessive dosage. These systemic effects, in turn, may cause a reversion to rapid shallow breathing, thus canceling the beneficial effects of the nebulization procedure.

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Physiologic Evaluation

In an effort to demonstrate by some objective means that the greater subjective benefit achieved by this improved method is the result of increased respiratory

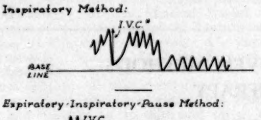

Figure 1. *Spirographic Tracing of the Breathing Pattern of a Severely Emphysematous Patient, Using (Top) the Inspiratory Nebulization Method (IM) As Contrasted with (Bottom) the Expiratory-Inspiratory-Pause Nebulization Method (EIPM).*

function, pulmonary function was studied before and thirty minutes after each of the two nebulization technics (IM and EIPM) described above. These studies were carried out either in the morning and afternoon of the same day or on successive days. The technic of nebulization and with the same nebulizer.‡

Table 1 presents data obtained by such a study of the two methods of nebulization in 8 patients with various severe respiratory disorders. All the patients had been taking nebulization therapy, using IM, before this investigation. It will be noted that the EIPM invariably produced a greater increase in measured functions, particularly those apt to be affected by obstruction of airways—that is, the expiratory vital capacity, one-second vital capacity and maximum breathing capacity.

Nebulization Apparatus

There are numerous commercially available nebulizers, many of which are known to be unsatisfactory because they do not produce a uniform aggregate of particles of the proper size. Studies by Dautrebande[5] have demonstrated that effective absorption depends much less on the concentration or physicochemical nature of a substance than on the size of the particles in a nebulized mist. Furthermore, the same author has shown that the aggregate of particles must be reasonably uniform; otherwise, smaller particles will collide with larger particles and cause precipitation, which, in turn, results in loss of particles from the

Table 1. *Effects of IM and EIPM Nebulization.*

Patient	Diagnosis	Inspiratory Vital Capacity with IM		Inspiratory Vital Capacity with EIPM		Expiratory Vital Capacity with IM		Expiratory Vital Capacity with EIPM	
		Before Bronchodilatation	After Bronchodilatation	Before Bronchodilatation	After Bronchodilatation	Before Bronchodilatation	After Bronchodilatation	Before Bronchodilatation	After Bronchodilatation
		liters	*liters*	*liters*	*liters*	*liters*	*liters*	*liters*	*liters*
H.H.*	Bronchial asthma	4.2	4.25	4.2	4.41	3.95	4.1	4.0	4.25
A.K.	Bronchitis	2.8	3.12	2.95	3.47	2.5	2.68	2.56	2.85
E.R.	Bronchial asthma	4.5	4.65	4.5	4.82	4.42	4.55	4.4	4.7
W.W.	Bronchitis	3.3	3.38	3.4	3.81	3.0	3.21	3.2	3.72
J.W.	Bronchial asthma	3.6	3.66	3.62	3.96	3.4	3.48	3.5	3.74
G.C.	Bronchiectasis	1.72	2.1	1.8	2.38	1.53	1.66	1.51	1.77
E.M.	Bronchitis	—	—	—	—	2.1	2.2	2.05	2.45
G.B.	Bronchitis	0.7	0.75	0.7	0.9	0.5	0.55	0.5	0.75
Mean		2.97	3.13	3.02	3.39	2.68	3.82	2.72	3.03
Mean increase		0.16		0.37		0.14		0.31	
p value		<0.05				<0.001			

*Only patient in group without emphysema.

tests were performed with a Collins 13-liter respirometer with appropriate corrections of the measured volumes to BTPS (body temperature, ambient pressure and saturated with water vapor).[7] The bronchodilator used in this and similar studies was either Aerolone compound* or Isuprel.† In each test the same total number of inhalations of drug was used by each nebulized mist. A tolerable range of particle size is 0.5 to 3.0 microns.

The particular device that should be used depends

*Aerolone (cyclopentamine and aludrine compound), kindly supplied by Eli Lilly and Company, Indianapolis, Indiana.

†Isuprel hydrochloride (isopropyl arterenol), kindly supplied by Winthrop-Stearns, Incorporated, New York City.

‡Vaponefrin nebulizer, available from Neosol Company, Incorporated, Upper Darby, Pennsylvania.

for the most part on the clinical status of the patient and the equipment available. Figure 2 shows one type of mask,* which gives satisfactory results in routine treatment. Figure 3 demonstrates an inexpensive face mask,† as modified for combination with a nebulizer. Both units are simple, sturdy devices that can be cleaned and maintained quite easily. The units are primarily for intermittent use but can be employed continuously by substitution of a continuous, reservoir type of nebulizer or by modification of a Vaponefrin nebulizer (Fig. 4) for this purpose. Figure 5 shows two types of devices for nebulization in connection with a tracheotomy. In emphysematous patients and in patients in respirators a commercial plastic unit (Fig. 5*A*) often does not fit properly. As a consequence, a simple plastic-tube unit (Fig. 5*B*) was devised. A curved tube of the same type was found more suitable for use on respirator patients. The apparatus is made from a piece of pliable plastic tubing‡ 10 to 15 cm. long. To one end is attached an ordinary length of corrugated tubing such as that used on anesthesia equipment. The other end of the corrugated tubing is attached to the nebulizer. A small hole, which can be stoppered, is cut above the tracheotomy opening to provide a simple means for suctioning the trachea. The hole that fits over the tracheotomy tube is cut to fit over its horns and thus to hold the plastic tube in place. It can further be secured with several heavy rubber bands (Fig. 5*B*).

All these nebulization devices require some form of gas under pressure to drive the nebulizer. Many different sources, in addition to bottled gas, have been used. Such items as small blower motors (hair dryers, paint sprayers and circulating fans) and suction pumps used in reverse have been successfully adapted for this purpose. If none of these are suitable or available hand-operated devices may be employed. The hand bulb can be used when only small quantities of medication are to be nebulized. When larger quantities of medication, such as mixtures of bronchodilators, wetting agents, antihistaminics and antibiotics, are to be nebulized, squeezing a hand bulb for the necessarily longer periods is often distressing. To remedy this situation, an automobile tire pump has been successfully employed to operate the nebulizer (Fig. 6*A* and *B*). The devices were designed primarily for home use. Several reservoir-type nebulizers§ now available produce a continuous aerosol mist for many hours without attention and are more suitable for use in the hospital or for prolonged nebulization. When such a reservoir unit is not available a "continuous-type" nebulizer can be made by modification of an ordinary Vaponefrin hand nebulizer, in the manner illustrated in Figure 4. This unit may be attached directly or indirectly by a length of corrugated tubing to any tent or mask unit.

Finally, perhaps the most effective method of nebu-

TABLE 1. *(Concluded).*

PATIENT	1-SEC. VITAL CAPACITY WITH IM		1-SEC. VITAL CAPACITY WITH EIPM		MAXIMUM BREATHING CAPACITY WITH IM		MAXIMUM BREATHING CAPACITY WITH EIPM	
	BEFORE BRONCHODILATATION	AFTER BRONCHODILATATION	BEFORE BRONCHODILATATION	AFTER BRONCHODILATATION	BEFORE BRONCHODILATATION	AFTER BRONCHODILATATION	BEFORE BRONCHODILATATION	AFTER BRONCHODILATATION
	liters	*liters*	*liters*	*liters*	*liters/min.*	*liters/min.*	*liters/min.*	*liters/min.*
H.H.*	1.2	1.35	1.25	2.6	96	117	100	133
A.K.	0.5	0.67	0.51	0.72	75	80	76	86
E.R.	2.0	2.1	2.05	2.5	85	88	83	99
W.W.	0.6	0.8	0.68	1.0	60	78	65	86
J.W.	1.0	1.1	1.0	1.95	80	92	80	102
G.C.	0.3	0.35	0.3	0.5	38	40	39	49
E.M.	0.5	0.45	0.45	0.65	30	35	29	41
G.B.	0.2	0.25	0.22	0.3	13	16	14	20
Mean	0.79	0.88	0.81	1.20	59.6	68.3	60.2	77.0
Mean increase	0.09		0.39		8.7		16.8	
p value	<0.005				0.005			

*Only patient in group without emphysema.

*OEM oxygen-therapy mask, available from Oxygen Equipment Manufacturers, New York City.

†NCG No. 24424 or 24451, available from National Cylinder Gas Company, Chicago, Illinois.

‡Tygon tubing No.S-22-1, obtainable from E. H. Sargent Company, Dallas, Texas.

§Humidimatic Nebulizer, available from John Bunn Corporation, Buffalo, New York; Mista Fog Nebulizer, available from Stanley Supply Company, Dallas, Texas; Mist O_2 Gen Nebulizer, available from Production Foundry Corporation, Oakland, California; NCG-Humidifier-Nebulizer, available from National Cylinder Gas Company, Dallas, Texas; Vapojette, available from Air-Shields, Incorporated, Hatboro, Pennsylvania.

lization currently available is the use of an intermittent positive pressure breathing (IPPB) apparatus. Motley et al.,[8] Smart and his colleagues[9] and Segal and his co-workers[10] reported on this device, which appeared to be superior to others. In an effort to determine the

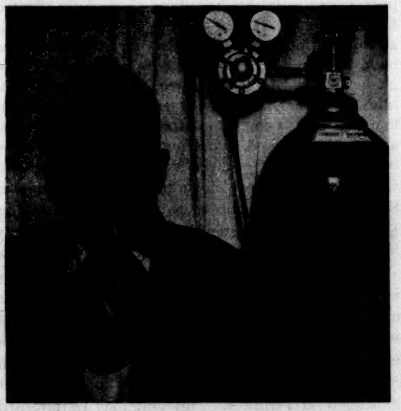

FIGURE 2. *OEM Mask with the DeVilbiss Nebulizer for Intermittent Nebulization Therapy in Upright* (A) *and Supine* (B) *Positions.*

specific effects of IPPB quite apart from those of bronchodilator substances that are usually adminis-

FIGURE 3. *Inexpensive ("Expendable") Face Mask Modified by Tying a Piece of Corrugated Anesthesia Tubing into the End of the Balloon So As to Provide Another Means of Continuous or Intermittent Nebulization Therapy.*

tered by the IPPB apparatus, Wu and her associates[11] studied the action of IPPB alone, bronchodilator alone and IPPB in addition to a bronchodilator. These studies indicated that for patients with obstructive ventilatory insufficiency IPPB with bronchodilator offers the best combination of therapy. Fowler, Helmholz and Miller,[12] in experiments designed to evaluate the more lasting effects of IPPB therapy in ambulatory patients with emphysema, concluded that IPPB with an aerosol bronchodilator offers no particular advantage over an aerosol bronchodilator that is used alone and efficiently. They added, however, that in the more seriously ill patients the assistance offered by the IPPB device provides a definite advantage.

AEROSOL MEDICATIONS

Bronchodilator substances are the principal drugs administered by the nebulization method. When ad-

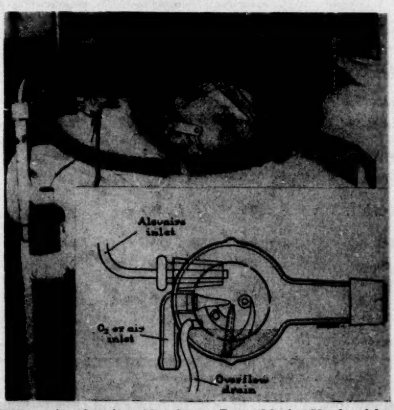

FIGURE 4. *Comfortable Open Face Mask, Used with a Modified Vaponefrin Nebulizer (Inset), for Continuous Nebulization Therapy.*

ministered by the EIPM described above, nebulized bronchodilators* provide the simplest and best means

*I have found Aerolone compound, Isuprel and Vaponefrin the most satisfactory bronchodilators.

of producing and maintaining bronchodilatation. This technic, in my experience, has eliminated a large number of the so-called drug-fast cases.

It is known that for an aerosol bronchodilator to be optimally effective, maximum penetration and retention of the drug must be achieved promptly, before systemic overdosage results from persistent but less effective use of nebulization procedures.[6] Many inveterate users of the "epinephrine needle" have been converted to nebulization of bronchodilators by the EIPM.

The use of a surface active agent such as Triton WR-1339* is currently a very satisfactory method of wetting the tracheobronchial tree and thinning viscid mucopurulent secretions.[13-16] This substance (Alevaire) must be used in liberal quantities when thick, tenacious tracheobronchial secretions are present. Such wetting agents have been found to be of particular value when combined with bronchodilators and, in certain cases, with antihistaminics.

Recently, Roettig et al.,[17,18] as well as others,[19-22] reported on the usefulness of Tryptar aerosol† in the management of intractable cases of chronic bronchopulmonary disease with excessive obstructing secretions. I have found Tryptar aerosol also to be valuable in the treatment of resistant infections due to *Aerobacter aerogenes* or *Pseudomonas aeruginosa*. In these conditions optimal tracheobronchial cleansing is desired. Effective bronchial drainage is an essential step in the control of these infections, which are frequently resistant to antibiotics and chemotherapeutic agents. Because trypsin is a potentially irritating substance to the upper respiratory tract its use is perhaps best advocated when diligent but more conservative measures fail to give the desired results. Liberal administration of bronchodilator and wetting-agent aerosols, when combined with postural drainage and effective coughing, often accomplishes the desired purpose without trypsin. Occasionally, continuous nebulization is necessary to produce adequate wetting of the tracheobronchial tree and thinning of viscid secretions.

Antibiotics were formerly extensively administered by nebulization. This is not now generally recommended. There is increased danger of sensitization, particularly with penicillin, when the drugs are topically applied, and there is no convincing evidence that the nebulization route is any more effective than the oral or parenteral route of administration of present-day preparations of antibiotics.[23] Polymixin B and streptomycin, both of which are generally given by injection, can be effectively administered in smaller doses by nebulization. Oxytetracycline occasionally cannot be tolerated by mouth. Under these circumstances it is usually effective in smaller nebulized doses for the treatment of bronchial infections caused by oxytetracycline-sensitive organisms. However, there are few circumstances in which it would not be possible to administer these substances in the conventional manner.

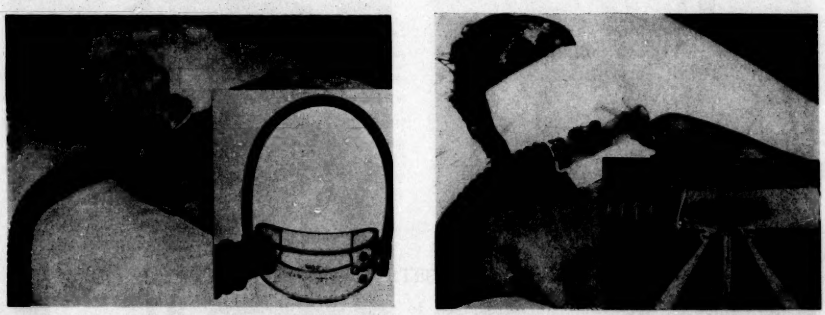

FIGURE 5. *Devices for Nebulization in Connection with a Tracheotomy, Showing Commercial Plastic Tracheotomy Mask Secured by a Length of Ordinary Rubber Tubing* (A) *and Tygon Plastic-Tube Tracheotomy Mask* (B).

EVACUATION OF SECRETIONS

Liquefaction or wetting of retained secretions results in an increase in the volume of material in the tracheobronchial tree until such secretions are eliminated. Failure to recognize this has led to the mistaken impression that aerosols of wetting agents or trypsin have made patients worse. It is true that, if such wetted secretions are not promptly liberated by effective coughing or suctioning, obstructive dyspnea will increase. The necessity for diligent attention to this effect of therapy should in no way serve as a contraindication to its use. Simply reminding the patient to cough will suffice to obtain clearing of secretions in many cases; frequently, however, tracheal aspiration is necessary, and in rare cases one may have to resort to bronchoscopic instrumentation or tracheotomy.

*Triton WR-1339, the active agent of Alevaire, available from Winthrop-Stearns, Incorporated, New York City.

†Tryptar aerosol, available from Armour Laboratories, Chicago, Illinois.

When patients are troubled with considerable amounts of thick, tenacious bronchial secretions, nebulization treatments should be given as frequently as necessary to facilitate the evacuation of inspissated material. This may mean continuous nebulization. In any event, such patients should take their treatments in a 15° to 18° Trendelenburg position, using the EIPM for breathing and at the same time combining these treatments with diaphragmatic breathing material are discussed. Evidence is presented that greater subjective and objective improvement results from the use of an expiratory-inspiratory-pause method (EIPM) of inhalation than from that of an inspiratory method (IM).

The details of the EIPM are described. The value of a slow respiratory rate and an inspiratory pause in enhancing the penetration and absorption of nebulized medications is emphasized.

FIGURE 6. *Use of an Automobile Tire Pump for the Operation of a Hand Nebulizer* (A) *and for Combination with a Modified NCG Expendo Mask in Patients Who Are Unable to Co-operate* (B).

exercises[24,25] and occasional voluntary coughing efforts; the coughing is quite important since these patients often have a diminished cough reflex and if not reminded to cough they will retain considerable secretions.

Tracheal aspiration frequently produces remarkable benefit. Even if direct tracheal aspiration is not successful the attempt will stimulate a more effective cough. For nebulized bronchodilator drugs to be most effective, clearing of tracheobronchial secretions is mandatory.

SUMMARY

Two different methods of inhalation of nebulized material are discussed. Evidence is presented that greater subjective and objective improvement results from the use of an expiratory-inspiratory-pause method (EIPM) of inhalation than from that of an inspiratory method (IM).

The details of the EIPM are described. The value of a slow respiratory rate and an inspiratory pause in enhancing the penetration and absorption of nebulized medications is emphasized.

Several different types of nebulization apparatus are illustrated, and their specific uses discussed. A mask nebulization unit is recommended for general use when gas under pressure is available. The automobile tire pump is suggested for use in outpatient treatment when large quantities of material are to be nebulized. A simple modification of the Vaponefrin nebulizer as a reservoir type of nebulizer is illustrated.

Specific aerosol medications and their application are discussed. Sympathomimetic bronchodilators, wetting agents, antihistaminics and trypsin are recommended in the presence of specific indications. The use of antibiotics by the aerosol method is not generally recommended.

The importance of maintaining a relatively clean tracheobronchial tree to control bronchial infections is emphasized. To achieve this end the nebulization of bronchodilator and wetting-agent mixtures in liberal quantities is recommended in conjunction with postural drainage, diaphragmatic exercises and voluntary coughing efforts.

Since this paper was submitted for publication Salomon, Herchfus and Segal[26] have reported favorable results from the use of an aerosol of Pancreatic Dornase (available from Sharp and Dohme, Incorporated, Westpoint, Pennsylvania) in the treatment of cases of bronchopulmonary disease with obstructing mucopurulent secretions. This is a valuable therapeutic adjunct.

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EMBOLECTOMY FROM ARTERIES OF THE LOWER LIMBS

An Analysis of Fifteen Cases

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EMBOLISM to an arterial bifurcation is at best a clinical impression. Positive diagnosis depends on removal of the embolus. For this reason most papers on the subject have been limited to surgical cases. During the four-year period 1950-1953 I saw and treated conservatively a number of probable brachial and popliteal or tibial emboli without loss of life or limb. In the same period 15 embolectomies among 13 subjects were performed at the aortic, iliac and femoral bifurcations.

Except for collective reviews individual series have been small. Warren and Linton,[1] in 1948, reported 18 aortic, iliac and femoral embolectomies by several surgeons at the Massachusetts General Hospital during a ten-year period. In 1950 Haimovici[2] described 23 embolectomies at these levels seen at Mount Sinai Hospital and in private practice over a twenty-year period. A year later Veal and Dugan[3] discussed their experience with 11 cases, and in 1953 des Prez and Hubay[4] presented a study of 25 such embolectomies in eighteen years at University Hospitals, Cleveland, Ohio. A series of 15 cases in as short a period as four years therefore seems worthy of report.

*Surgeon-in-chief, Wesson Memorial Hospital; assistant visiting surgeon, Springfield Hospital; consultant vascular surgeon, Holyoke Soldier's Home, Holyoke, Massachusetts.

Diagnosis

The clinical diagnosis of arterial embolism of the lower limbs is not difficult, and can usually be made from the history alone: sudden pain, followed by paresthesias, coldness and early paralysis of the affected leg. The examiner feels no pulse at any point distal to the involved bifurcation, with a vigorous pulse coming down to it.

Differential Diagnosis

Description of the ischemic, cold, pulseless and paralyzed leg is unnecessary. That it may represent a surgical emergency should be emphasized. Clinical discovery of a source of embolism is a major factor in diagnosis. This cannot be entirely relied upon, however, and in 3 of the 13 patients under study successful embolectomy was performed in the absence of an apparent source. Two of these later proved to have sustained "silent" coronary occlusions. In the third patient, who had hypertension, sporadic runs of atrial

flutter not appreciated before embolectomy developed. By a process of elimination aortic plaques[5] are sometimes regarded as sources of emboli, though none were seen in this series. True paradoxical embolism through a cardiac septal defect is rare and was not found in any case.

Confusion arises with acute arterial thrombosis and also with thrombophlebitis with accompanying arterial spasm. No patients of this series, however, were explored without the finding of an embolus, and at the predicted bifurcation. Distinction from arterial thrombosis is academic, and when one is in doubt wisdom indicates exploration. In almost every case in this series the diagnosis was possible by the use of fingers and eyes alone. Occasionally, the oscillometer was an aid in an obese patient. It is not believed that aortography[6] is necessary or even desirable. That the femoral pulse is almost always palpated, and even accentuated, on the side of a femoral embolism is worthy of repeated emphasis. This is the commonest site of lodgment and therefore the most important to diagnose consistently.

TABLE 1. *Sites of Lodgment of Peripheral Arterial Emboli.*

SITE	FREQUENCY %
Femoral artery	54.4
Iliac artery	17.2
Axillary artery	11.8
Brachial artery	11.8
Popliteal artery	11.3
Aorta	4.5
Carotid artery	—
Subclavian artery	—

It caused confusion among several examiners in this series, with consequent delay in treatment.

Levels of skin mottling and temperature drop depend on the state of the collateral circulation around an embolus and are not, therefore, a reliable guide to the level of the block. Experience with this group of cases serves to emphasize again the fact that emboli of the lower limbs are usually higher than one thinks.

SITE AND SEX

The occurrence of 1 aortic, 3 iliac and 11 femoral embolectomies in this series is not at variance with the well known high frequency of femoral as compared with other sites of peripheral arterial embolism (Table 1).

There were 8 female and 5 male patients.

SOURCE

Eight patients underwent 9 embolectomies, the source of embolism being some variant of arteriosclerotic heart disease, either with atrial fibrillation (5 cases) or recent or past myocardial infarction (3 cases). Five patients underwent 6 embolectomies as a result of the embolic stage of rheumatic heart disease; all had mitral stenosis with atrial fibrillation. A sixth case, of embolizing rheumatic mitral stenosis and fibrillation not included in this study, was previously reported[7]; the left atrial appendage was ligated after a brachial embolism. The cardiac operation did not prevent an embolism of a minor tibial artery on the tenth postoperative day. Atrial thrombi are not confined to the appendage.

Storer and his associates[8] showed that atrial blood stasis due to mitral stenosis, combined with fibrillation, contributed the largest number of intra-atrial thrombi, and fibrillation alone the next largest. Least commonly found were thrombi within the atrium when mitral regurgitation was present to keep the atrial blood in a constant whirl. There were 5 patients in this series with atrial fibrillation of arteriosclerotic origin in whom atrial stasis due to mitral stenosis was not a factor. Since fibrillation alone is sufficient to produce thrombus in the atrium it seems unlikely that mitral valvulotomy (unless it causes significant regurgitation of blood in the atrium) can often prevent embolism when fibrillation has become established in rheumatic heart disease.

The 8 arteriosclerotic hearts among 13 sources of emboli in this series may have significance. Only 33 of 81 cases were found to have such a source in the series of Warren and Linton.[1] It will be interesting to observe whether future reports bear out an apparent trend away from the classic fibrillating rheumatic heart as a source of arterial emboli. That such a trend seems to be occurring is attested by the present study, and by two recent series (Table 2). It is possible that

TABLE 2. *Age Versus Etiology of Embolism.*

SOURCE	DATE	AVERAGE AGE OF PATIENTS	RHEUMATIC HEART DISEASE		ARTERIOSCLEROTIC HEART DISEASE	
		yr.	NO. OF CASES	PERCENTAGE	NO. OF CASES	PERCENTAGE
Warren & Linton[1]	1948	52	48	59.0	33	40.0
Haimovici[3]	1950	—	20	22.5	69	77.5
des Prez & Hubay[4]	1953	60	28	35.0	52	65.0
Present series	1954	60	5	38.5	8	61.5

this trend represents an expression not only of the increasing life span but also of the gradual disappearance of rheumatic heart disease in this era of antibiotic therapy of streptococcal infection.

AGE

The average age for this series was sixty years, as it was among 85 patients with emboli at all sites discussed by des Prez and Hubay.[4] This is to be compared with an average age of fifty-two years in the cases presented by Warren and Linton[1] (Table 2), who reported only 5 of a total of 95 patients with emboli to be in the age group of seventy-one to eighty years whereas almost that number (4) of 13 were in this advanced decade in the present study.

The age of the patient varied with the etiology of his disease (Table 3). Those with emboli of arteriosclerotic cardiac sources were in the majority and were

an average of eleven and a half years older than those with rheumatic heart disease.

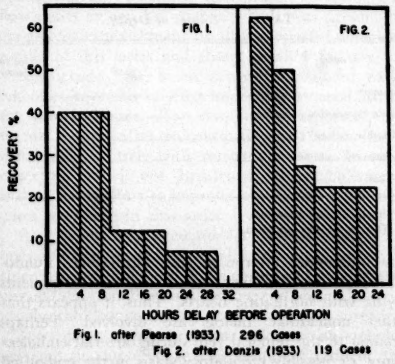
No patient was denied embolectomy because of his age or because his vessels were assumed to be too brittle or calcific. One of the most successful results in this series was obtained in the oldest person operated on. This was an eighty-year-old woman in whom complete restoration of pulses at all levels followed removal of an embolus at the left femoral bifurcation. Admittedly, greater care is required in temporary occlusion and suture of sclerotic arteries, but arteriosclerosis does not preclude successful embolectomy, and over half (5 of 9) the successes in the series were obtained in elderly patients with arteriosclerosis.

TABLE 3. *Age at Embolism.*

TYPE OF DATUM	AGE
	yr.
Average of 13 patients with 15 embolectomies	60
Extremes: Lowest	41
Highest	80
Arteriosclerotic heart disease (8 patients)	64½
Rheumatic heart disease (5 patients)	53

DURATION AND RESULTS

It is generally recognized that time is of the essence for success with embolectomy. There is a striking drop in limbs saved when embolectomy is delayed beyond eight hours (Fig. 1 and 2). Though eight hours is crucial, it is by no means an absolute or arbitrary time limit. More than occasional successes are possible ten hours after an embolism.



FIGURES 1 AND 2. *Relation of Time to Recovery in 415 Cases of Peripheral Arterial Emboli (Reproduced from Hopkins' with the Permission of the Publishers).*

Both figures show that the rate of recovery ranges between 40 and 60 per cent if the patient is operated on within the first eight hours. The rate drops sharply with delay beyond eight hours.

In this series of 15 embolectomies 2 occurring in 1 patient are not available for study since the patient died in uremia too soon for proper evaluation. At autopsy the embolectomized right iliac and left femoral arteries (Fig. 3) were found to be free of blood clot, but both renal arteries were completely blocked by emboli. Of the 13 remaining analyzable embolectomies in 12 patients 4, performed on 3 patients, were failures. There were no amputations, since all 3 patients died before amputation became necessary.

The first patient was operated on twenty hours after femoral-artery embolism, and it was impossible to free an adherent distal thrombus after the embolus had been removed. At autopsy this thrombus formed a solid cast of the distal arterial tree. The second failure resulted from fruitless attempts to remove an adherent aortic saddle embolus of forty-eight hours' duration. Retrograde maneuvers through bilateral femoral arteriotomies were used. The third failure followed inadvertent tearing of the intima during removal of an iliac embolus downward through a femoral approach. This desperately sick patient was in irreversible heart failure, had had two previous emboli and had sustained a brachial embolus at the time of her iliac one. On the operating table a fifth embolus struck the opposite femoral bifurcation; this was removed. At autopsy a sixth embolus was discovered at the popliteal bifurcation, in addition to phlebothrombosis on the right and pulmonary embolism.

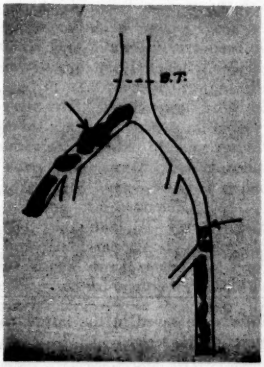


FIGURE 3. *Emboli in the Right Iliac and Left Femoral Arteries, with "Tail Clots" (Arrows) Removed from a Patient Who Died Too Soon for Proper Evaluation.*

At autopsy he was found to have sustained complete obstruction of both renal arteries by other emboli. "B.T." refers to a modified Bethune tourniquet used to occlude the abdominal aorta temporarily during "direct" removal of an embolus from the right iliac artery. The patient was seen within an hour of the multiple embolisms and was in good condition. Spinal anesthesia was used.

Nine patients underwent 9 successful embolectomies. This represents 70 per cent success among 13 analyzable cases and is compared to recently reported series in Table 4. Four of the 9 patients had rheumatic, and 5 had arteriosclerotic heart disease. The 9 successes were obtained an average of four and three-quarters hours after embolism. The longest interval between embolism and successful embolectomy was twelve hours, and the shortest two hours. All but 2 cases seen within twelve hours were successful,

TABLE 4. *Results of Aortic, Iliac and Femoral Embolectomies.*

SOURCE	DATE	NO. OF EMBOLECTOMIES	LIMBS SAVED	HOSPITAL MORTALITY	REMARKS
			%	%	
Key[10]	1936	44	50.0	39.5	
Lund[11]	1937	—	47.4	44.4	
Reynolds & Jirka[12]	1944	—	—	75.0	Under 18 hr. all limbs saved
Warren & Linton[1]	1948	18	83.4	28.6	Under 11 hr. all but 1 limb saved (10-yr. period)
Haimovici[2]	1950	23	43.5	60.8	(20-yr. period)
Veal[3]	1951	11	90.0	20.0	All cases seen within 8 hr.
des Prez & Hubay[4]	1953	25	84.0	16.0	(18-yr. period)
Present series	1954	15	70.0	46.1	Under 12 hr. all but 2 limbs saved (4-yr. period)

and all limbs were saved in the last 7 consecutive embolectomies of the series.

ANESTHESIA AND METHOD OF EMBOLECTOMY

Spinal anesthesia was used in 1 case with emboli in the right iliac and left femoral arteries. The embolus in the right iliac artery was removed directly through a retroperitoneal-iliac approach. All the remaining embolectomies of the series were performed through a femoral approach, either directly (for femoral emboli) or by retrograde maneuvers (for 2 iliac and 1 aortic emboli). As one might have expected, no anesthesia at all was necessary in 1 desperately ill patient in whom late aortic embolectomy was attempted via bilateral femoral arteriotomies. All remaining 12 embolectomies were performed under novocain anesthesia.

Thus, there is a minimal anesthetic risk in most embolectomies involving the lower limbs. Direct aortic and iliac approaches requiring general anesthesia should be reserved for the relatively few fair-risk patients with these lesions who are seen early after embolism before shock becomes irreversible.

MORTALITY

Six of 13 patients in the series died, making a hospital mortality rate of 46.1 per cent. This is compared to other recent series in Table 4. Attention is again called to the unusually elderly arteriosclerotic patients predominating in this study. All had severe, often terminal, heart disease. No patient, however, was denied operation because of these facts, and none of the 6 deaths were related to the surgery performed.

Autopsy was performed in all but 1 fatal case (listed as "cardiac failure" in Table 5). The verified causes of death (Table 5) are especially interesting in that 3, or half the patients, had proved terminal pulmonary embolism. One of these also had multiple silent (and clinically unrecognized) duodenal ulcers, with massive gastrointestinal hemorrhage from one ulcer, and acute perforation of another. Such a high frequency of fatal pulmonary embolism among embolectomized patients has not been previously reported.

If pulmonary embolism so often accompanies major arterial embolism and embolectomy in the lower limb it is interesting to speculate about the mechanisms involved and possible means of preventing this complication. All the patients who died of pulmonary embolism were receiving anticoagulants at the time of death. Thus, prothrombin levels in the therapeutic range did not prevent fatal pulmonary embolism. This complication is not, of course, uncommon among such elderly bed-ridden, cardiac patients as predominated among the subjects of this report. In concentrating on the left atrium one is apt to forget that the right, communicating with

TABLE 5. *Causes of Death.*

CAUSE	NO. OF CASES
Uremia*	1
Acute myocardial infarction	1
"Cardiac failure"†	1
Pulmonary embolism	3
Total	6

*Bilateral renal embolisms.
†Only death not autopsied.

the pulmonary arteries, is also fibrillating. Pulmonary embolism, however, does not kill half the patients dying with fibrillating hearts. Thus, it appears that other noncardiac factors are involved. Perhaps trauma to the femoral vein during arterial embolectomy, or possibly circulatory stasis in the embolized leg, is at fault.

Haimovici[2] pointed out that venous thrombosis concurrent with arterial embolism had received little attention in the literature, and noted it in 24 of 330 cases. He believed that the thrombosis arose by transverse propagation of inflammation from the embolized arterial wall to the adjacent vein. Phlebothrombosis was seen in 2 patients in the present series — in 1 dying of pulmonary embolism and in another, months after successful embolectomy, who had never had pulmonary embolism. It is understand-

able that, as in 2 autopsied cases with associated pulmonary embolism, one may fail to find deep femoral-vein thrombosis, the clot having already left the leg. Complete dissection of the leg veins into the distal reaches was not performed in these autopsies.

When they were used in this series anticoagulants were administered primarily in an effort to prevent re-embolism and not because of any particular concern about postoperative thrombosis at the arteriotomy suture line. They were not used in 3 successful embolectomies because, at sixty-six, sixty-eight and eighty years of age, respectively, these patients were considered too elderly and arteriosclerotic or unreliable for use of such potentially dangerous drugs.

One wonders whether, since adequate anticoagulant therapy did not prevent them, pulmonary emboli should not be anticipated by routine interruption of both distal femoral veins at the time of arterial embolectomy in the lower limbs.

Retrograde Flow

The necessity of clearing the distal arterial tree of "tail clot" at the time of embolectomy has been emphasized.[1-3,13] This maneuver, when successful, establishes retrograde arterial blood flow not already present. One can almost predict a successful outcome, barring technical difficulties, if retrograde flow exists or can be established. It was present or capable of establishment in all 9 successful embolectomies of this series and absent in all 4 failures.

Retrograde flow is an accompaniment of early embolectomy, and is often impossible to establish in the very late case. The rare success reported[14] up to two months after embolism depends on an intact distal arterial tree with retrograde flow. In such cases the limb is not threatened, and embolectomy is done in an effort to improve leg function. No such cases were seen in this series.

Retrograde flow accounts for success when nonoperative treatment of arterial embolism is employed since it depends on and is a measure of the collateral circulation around an obstructing embolus. Unfortunately, the flow cannot be predicted before surgery.

Incomplete circulatory obstruction by an embolus was not encountered in this series. Spasm of the distal artery before manipulation was often pronounced. In a few cases it was minimal, as evidenced by an almost immediate ballooning of the distal artery to normal caliber when the blood flow was re-established after embolectomy.

It is worthy of note that retrograde flow was found at operation to be poor to absent in 2 of the 3 patients in this series who died of pulmonary embolism. The third patient with fatal pulmonary embolism had a good retrograde flow and a successful embolectomy. However, she had sustained a previous femoral-artery embolism in the opposite leg, for which she was not seen and for which midthigh amputation had been performed ten days previously. Thus, the implication of venous stasis accompanying poor to absent (retrograde) arterial blood flow becomes almost inescapable among the patients in this study who died of pulmonary embolism.

Summary and Conclusions

Embolectomy is safe and is the treatment of choice at the aortic, iliac and femoral bifurcations. Nine (70 per cent) successes were obtained among 15 embolectomies in 13 unselected patients during a four-year period. Despite a 46 per cent hospital mortality no patient died as a result of operation, and no limbs were lost in the last 7 embolectomies.

Fingers and eyes alone will diagnose most cases. No patient was explored without the finding of the embolus, and at the predicted bifurcation. In the most frequent site, the femoral bifurcation, both femoral pulses were palpable in all cases. This fact was not sufficiently realized by some examiners, with resultant delay in treatment. The embolus was successfully removed in 3 cases without evident cardiac source at the time of operation.

Anesthetic risk is minimal. For the vast majority of lower-limb embolectomies novocain alone is required. Occasional direct aortic and iliac embolectomy requiring general anesthesia should be reserved for the fair-risk patient seen early before irreversible shock appears.

Embolectomy should not be denied a patient merely because he is very old and arteriosclerotic. Eight of 13 embolectomies, as well as 5 of 9 successes, were in the elderly arteriosclerotic patients. Four were performed in patients seventy-one to eighty years of age. There appears to be a recent trend away from the classic fibrillating rheumatic heart as a source of emboli.

Embolectomy should be performed within eight hours whenever possible; it should not be abandoned, however, because a supposed, arbitrary "deadline" has been exceeded after embolism. More than occasional successes are obtained after eight hours. All but 2 cases seen within twelve hours were successful.

Retrograde blood flow has tremendous prognostic significance. It was present or capable of establishment in all cases seen early and in all 9 successes. It was absent in all 4 failures, and was absent in 2 of 3 cases of fatal pulmonary embolism.

Consideration of routine femoral-vein interruption with lower-limb embolectomy is warranted, since half the deaths (3 of 6) in this series were from pulmonary embolism despite adequate anticoagulation. Such a high frequency of fatal pulmonary embolism among embolectomized patients, it is believed, has not previously been reported.

6 Temple Street

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THE ADVERSE EFFECTS OF BELLADONNA ALKALOIDS IN BENIGN PYLORIC OBSTRUCTION*

An Experimental Study

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BELLADONNA alkaloids are frequently prescribed in the treatment of patients with chronic peptic ulcer, including those with the complication of gastric retention.[1,2] The rationale underlying such therapy is usually developed as follows: gastric retention is the result of pyloric stenosis; pyloric stenosis is caused to a variable degree by antral or pyloric spasm; gastrointestinal spasm is said to be inhibited by belladonna alkaloids; and therefore, belladonna alkaloids lessen the degree of pyloric stenosis and benefit gastric retention. This chain of reasoning, however, ignores the fact that the size of the pyloric outlet is only one determinant affecting gastric evacuation. Others are the intraluminal gastric pressure produced by gastric tone and peristalsis and the gastroduodenal pressure gradient, which depends on pressure within the duodenum as well as within the stomach. In normal subjects, as a matter of fact, gastric evacuation has been shown to depend principally on the character of gastric tone and peristalsis; the role of the sphincter is relatively minor.[3-6]

The normal physiology of gastric emptying must also be considered in patients who are suffering from benign pyloric obstruction with gastric retention. As long as gastric tone and active peristalsis are present, gastric retention is not excessive although the pyloric canal may be extremely narrow. The gastric hyperperistalsis frequently described by the radiologist in patients with early pyloric obstruction demonstrates the compensatory effort of gastric motility in the face of pyloric stenosis. If the obstruction persists, however, the stomach becomes fatigued, peristalsis diminishes and atony supervenes. The stomach can now be said to be entering a decompensated stage and gastric retention occurs. It is in this later stage that the classic symptoms and findings of gastric retention appear: vomiting of retained food, clapotage and so forth.

Since gastric evacuation depends to such a great degree on effective gastric motility it is clear that any agent that inhibits the motor power of the stomach may aggravate rather than lessen the degree of retention. The alleged inhibitory effect of the belladonna alkaloids on spasm associated with inflammation is purely theoretical; it is a hypothetical effect that has never been demonstrated. On the other hand belladonna alkaloids have been shown to inhibit gastric tone and peristalsis.[7,8] For these reasons the rationale of using belladonna alkaloids in chronic benign pyloric obstruction may be seriously questioned. The following study was conducted to obtain experimental data on the effect of belladonna alkaloids on gastric evacuation in patients with benign pyloric obstruction.

Method of Study

The effect of several belladonna alkaloids on gastric emptying was studied in two groups of subjects. One group consisted of patients with duodenal ulcer who either recently or at some time in the past had had clinical and x-ray evidence of pyloric obstruction with gastric retention. The second group was composed of either subjects with no disease or patients with functional gastrointestinal disorders, healed gastric ulcer and active or healed duodenal ulcers without obstruction.

In both groups the procedure of study was the same. A control observation was made without medication: each patient was given 200 cc. of a barium-water mixture, and the rate of emptying was determined radiographically. On another day the examination was repeated, but medication in the form of atropine 0.6 mg. subcutaneously, Bellafoline,‡ 0.5 mg. subcutane-

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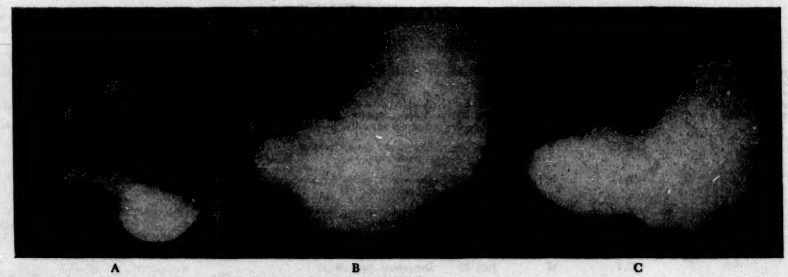
‡Bellafoline, available from Sandoz Chemical Works, New York City, consists of the total levorotatory alkaloids of belladonna leaves.

ously, or tincture of belladonna, 12 to 15 drops by mouth, was administered fifteen to thirty minutes before the barium drink. Fluoroscopic examinations were made immediately after the barium swallow, at hourly intervals when feasible and at five hours unless the stomach had emptied in the meantime. Usually, the control study and the study after medication were conducted within a period during which no obvious clinical changes had taken place; a number of patients were also observed repeatedly for several months. The amount of barium in the stomach was estimated at each observation and expressed as the percentage of ingested barium. Barium in the stomach five hours after ingestion was considered to indicate gastric retention. The term "delayed emptying" was used to signify that the medication prolonged the emptying time but without causing five-hour retention.



A B C

FIGURE 1. *Effect of Bellafoline on Gastric Emptying in Pyloric Obstruction (Patient T.M., Table 1).*
A=*x-ray film taken during the control study five hours after the barium swallow. A peristaltic wave can be seen. Retention was estimated at 10 to 15 per cent.*
B=*x-ray film taken immediately after the barium swallow (the patient had received Bellafoline, 0.5 mg. subcutaneously fifteen minutes before the swallow). The stomach is atonic, and no peristalsis is seen.*
C=*x-ray film taken five hours after B. A slight increase in tone and a feeble peristaltic wave are observed, but no gastric emptying has occurred.*

RESULTS

Group A

Patients with chronic duodenal ulcer and pyloric obstruction (Table 1) were arbitrarily divided into four subgroups, depending on the clinical features of the case.

Subgroup 1. In this subgroup patients with symptomatic pyloric obstruction who had been recently treated by continuous gastric suction (8 patients) had been admitted to the hospital because of clinical evidence of pyloric obstruction with gastric retention as manifested by abdominal pain, vomiting, clapotage and presence of retained food in a fasting gastric aspiration. Continuous gastric suction had been maintained for three or four days immediately before the barium study. As a result of this regimen gastric tone and peristalsis frequently returned to normal so that at the time of study five-hour retention was often absent.

The control, premedication observation in 4 of the 8 patients did not show any five-hour retention. Of the others 3 patients had 10 to 25 per cent retention at five hours, and the fourth had 10 per cent retention in one study and none in a subsequent examination.

Observation after medication demonstrated either a delayed emptying or minor degrees of retention in the first 4 patients and a great increase in retention, varying between 50 and 100 per cent, in the latter 4 (Fig. 1).

Subgroup 2. These 3 patients with symptomatic pyloric obstruction not treated by gastric suction had clinical evidence of gastric retention of a minor degree so that continuous aspiration therapy was not considered necessary. One of the patients (M.F.) was also observed at repeated intervals when he was free of symptoms; gastric emptying at these times was within normal limits.

In the postmedication study of these 3 subjects 20 per cent retention was observed in 2; in the third (M.F.), mentioned above, 100 per cent retention was produced when he had symptoms but only 25 to 30 per cent retention when he was without symptoms.

Subgroup 3. This patient with chronic stationary retention but without symptoms had been given x-ray examinations at frequent intervals over a period of seven years. Fifty per cent retention at five hours was always present. During the study, whenever medication was given, the retention increased to 90 or 100 per cent.

Subgroup 4. These 3 patients, who had a past history of pyloric obstruction but were asymptomatic at the time of study, had been treated for pyloric obstruction by continuous gastric suction at some time in the past. No five-hour retention was noted in the control observation, but after medication a delayed emptying occurred in 2 subjects and a 25 per cent retention in the third.

The impaired gastric evacuation of barium that oc-

curred in all four subgroups after the belladonna alkaloids was associated with diminished to absent gastric peristalsis and a flabby-appearing stomach.

Group B

Patients without pyloric obstruction (Table 2) were examined to determine whether the previously described effect of the belladonna alkaloids on gastric emptying occurred in all patients or only in those with previously impaired gastric motility—that is, patients with gastric retention.

Subgroup 1. Three subjects without disease were studied. Gastric emptying was complete in two hours. After the belladonna alkaloids a delay was observed in 2 subjects and 15 per cent retention at five hours in the third.

Subgroup 2. Study of 5 patients with functional gastrointestinal disorders revealed no effect in 2 subjects, a delayed gastric emptying in 2 and a 25 per cent retention in the fifth.

Subgroup 3. Of these 7 patients with either active or healed peptic ulcers but without obstruction the belladonna alkaloids had no effect in 4 and produced minor degrees of five-hour retention in 3.

The delay in gastric emptying or retention produced by the belladonna alkaloids was again associated with diminished peristalsis as judged fluoroscopically.

TABLE 1. *Summary of Data on the Effects of Belladonna Alkaloids in Patients with Chronic Duodenal Ulcer and Pyloric Obstruction (Group A).*

CLINICAL STATUS AT TIME OF STUDY	PATIENT	SEX	DATE	RADIOGRAPHIC CONTROL OBSERVATION					
				TONE & PERISTALSIS IMMEDIATELY AFTER SWALLOW	BARIUM IN STOMACH AT				
					END OF 1ST HR.	END OF 2D HR.	END OF 3D HR.	END OF 4TH HR.	END OF 5TH HR.
					%	%	%	%	%
Subgroup 1 (symptomatic pyloric obstruction recently treated by continuous gastric suction)	L.D.	M	Mar. 29	Normal tone; hyperperistalsis.					0
	W.F.	M	Jan. 6	Atonic; no peristalsis.	100	100			0
			Jan. 20	Atonic; occasional peristalsis.		0			
			Sept. 9	Normal tone and peristalsis.					0
	G.C.	F	Feb. 2	Decreased tone; normal peristalsis.			1		
	R.G.	M	Mar. 28	Decreased tone; hyperperistalsis.	5	0			
	T.M.	M	Jan. 19	Decreased tone; hyperperistalsis.					10-15
			Jan. 24	Normal tone & peristalsis			1		
	C.T.	M	July 23	Decreased tone & peristalsis	80				40
	M.B.	M	Dec. 4	Normal tone & peristalsis	40	30		25	20-25
	H.D.	M	May 5	Decreased tone; no peristalsis.	100	40	25	25	15
Subgroup 2 (symptomatic pyloric obstruction not treated by suction)	R.O.	F	Feb. 7	Normal tone; occasional peristalsis.	40	25	20	20	10
	A.M.	F	Mar. 6	Atonic; normal peristalsis.	100		0		
	M.F.	M	Apr. 7	Atonic; occasional peristalsis.					2-3
			June 20	Atonic; moderate peristalsis.		0			
			July 25	Atonic; moderate peristalsis.	100		0		
Subgroup 3 (chronic pyloric obstruction without symptoms)	E.L.	F	May 16	Atonic; normal peristalsis.	100	100	100		50
			July 5	Atonic; normal peristalsis.					40-50
Subgroup 4 (past history of pyloric obstruction but asymptomatic)	H.F.	M	May 17	Normal tone; hyperperistalsis.					0
	W.M.	M	Apr. 11	Normal tone; hyperperistalsis.	3				
	D.K.	F	Jan. 3	Normal tone & peristalsis		0			

DISCUSSION

Previous investigations concerning the influence of atropine on gastric evacuation were done mainly in normal subjects, rarely in patients with pyloric obstruction. In addition the reported results in normal persons were contradictory: no effect was noted in some,[9,10] a delayed emptying was observed in others,[7,8] and still others showed an increased rate of gastric evacuation.[11,12]

The studies on the effects of the belladonna alkaloids in patients with and without an episode of pyloric obstruction discussed above revealed that clinical doses delayed gastric emptying in the majority and produced a significant gastric retention in some. These results were most apparent in patients with chronic duodenal ulcer with pyloric obstruction (Group A, Table 1). Thus, all these 15 patients experienced prolongation of gastric emptying time, with five-hour retention in 9 of the 15, 4 of whom had 100 per cent retention. In general the degree of prolongation by the belladonna alkaloids was related to the clinical state of the disease. Observations on 2 patients, W.F. and M.F., who were studied over four and nine months respectively, illustrate this point. When they had symptoms of obstruction the medication produced retention; when they were asymptomatic the effects of the drug were negligible. It was apparent from these observations that, regardless of possible favorable changes on pyloric "spasm," the inhibitory action of the belladonna alkaloids on gastric motility was predominant.

Certain objections can be raised concerning the method of study. First of all, the method employed is not completely physiologic—that is, the response to a barium meal only simulates the events that occur in gastric secretion and motility after the ingestion of food. Secondly, estimation of the amount of barium in the stomach by radiographic technic can only be approximate at best. And, finally, no account is taken of the possible alteration in the volume of gastric juice by the belladonna alkaloid.

The first objection cannot be refuted completely, but in general gastric retention, as judged clinically, and the rate of gastric evacuation, as judged by usual gastrointestinal radiologic technic, show an adequate degree of parallelism. Regarding the second objection

TABLE 1 *(Concluded)*.

DATE	DRUG	RADIOGRAPHIC OBSERVATION AFTER MEDICATION					
		TONE & PERISTALSIS IMMEDIATELY AFTER SWALLOW	BARIUM IN STOMACH AT				
			END OF 1ST HR.	END OF 2D HR.	END OF 3D HR.	END OF 4TH HR.	END OF 5TH HR.
			%	%	%	%	%
Apr. 2	Bellafoline (0.5 mg. subcutaneously)	Moderate tone; decreased peristalsis.		100			15-20
Jan. 13	Bellafoline	Atonic; occasional perstalsis.					25-30
Jan. 27	(0.5 mg. subcutaneously	Atonic; occasional perstalsis.					20-25
Aug. 4	on each date)	Normal tone & peristalsis			50	0	
Feb. 3	Atropine (0.6 mg. subcutaneously)	Slightly atonic; decreased peristalsis.					1-2
Apr. 1	Atropine (0.6 mg. subcutaneously)	Atonic; moderate peristalsis.	80		20	5	0
Jan. 22	Bellafoline (0.5 mg. subcutaneously)	Atonic; no peristalsis.					100
Jan. 29	Atropine (0.6 mg. subcutaneously)	Slight tone; moderate peristalsis.					100
July 26	Bellafoline (0.5 mg. subcutaneously)	Atonic; no peristalsis.					100
Dec. 6	Atropine (0.6 mg. subcutaneously)	Atonic; no peristalsis.	60			60	50
May 6	Atropine (0.6 mg. subcutaneously)	Atonic; no peristalsis.					50
Feb. 28	Bellafoline (0.5 mg. subcutaneously)	Atonic; no peristalsis.				20	20
Mar. 14	Atropine (0.6 mg. subcutaneously)	Atonic; occasional peristalsis.	100		75		20
Apr. 11	Bellafoline (0.5 mg. subcutaneously)	Atonic; no peristalsis.			100		100
May 25	Atropine (0.6 mg. subcutaneously)	Atonic; occasional peristalsis.					30-35
Aug. 8	Tincture of belladonna (12 drops)	Atonic; decreased peristalsis.	100		90	40	25-35
May 18	Atropine (0.6 mg. subcutaneously)	Atonic; no peristalsis.					90
July 18	Atropine (0.6 mg. subcutaneously)	Atonic; no peristalsis.					100
Sept. 5	Tincture of belladonna (15 drops)	Atonic; no peristalsis.					100
May 19	Bellafoline (0.5 mg. subcutaneously)	Normal tone & peristalsis					25
Apr. 18	Atropine (0.6 mg. subcutaneously)	Atonic; occasional peristalsis.	50	15	5	3	0
Jan. 10	Bellafoline (0.5 mg. subcutaneously)	Decreased tone & peristalsis		60	15	15	0

each subject acted as his own control; consequently, any error that might occur in the estimation of the amount of barium in the stomach at any one time would probably be of equal magnitude in the studies before and after medication. Finally, it may be argued that the inhibitory effect of atropine on the rate of gastric secretion is so beneficial that any associated results outlined above indicate that anticholinergic agents may at times aggravate gastric retention in patients with partial pyloric obstruction. Consequently, if such patients are given anticholinergics they should be followed carefully for signs of increasing gastric retention. If these signs develop, or if the patient in general fails to respond to the prescribed regimen as promptly as might be expected, the anticholinergic agents should be discontinued.

TABLE 2. *Summary of Data on the Effects of Belladonna Alkaloids in Patients without Pyloric Obstruction (Group B).*

STATUS	PATIENT	AGE	SEX	RADIOGRAPHIC CONTROL OBSERVATION					
				TONE & PERISTALSIS IMMEDIATELY AFTER SWALLOW	BARIUM IN STOMACH AT				
					END OF 1ST HR.	END OF 2D HR.	END OF 3D HR.	END OF 4TH HR.	END OF 5TH HR.
		yr.			%	%	%	%	%
Subgroup 1 (no disease)	B.J.	22	F	Normal tone & peristalsis	20	0			
	P.S.	22	F	Normal tone & peristalsis	50	0			
	G.P.	25	F	Normal tone & peristalsis	10	0			
Subgroup 2 (functional gastrointestinal disorder)	R.B.	60	F	Normal tone & peristalsis	0				
	N.M.	28	M	Decreased tone & peristalsis	50		0		
	A.V.	40	M	Normal tone & peristalsis	0				
	F.S.	38	F	Decreased tone & peristalsis					5
	R.A.B.	63	M	Normal tone & peristalsis	0				
Subgroup 3 (healed or active peptic ulcer)	G.D.	50	M	Atonic; normal peristalsis.					0
	J.S.	61	M	Normal tone & peristalsis			0		
	A.H.	68	M	Normal tone & peristalsis		0			
	A.G.	48	M	Normal tone & peristalsis		0			
	R.D.	50	M	Normal tone & peristalsis		50	2		
	C.G.	50	M	Normal tone & peristalsis		0			
	R.S.	38	F	Normal tone & peristalsis	30	0			

inhibition of gastric motility may be discounted. However, studies by Crocker[13] with a dye-dilution technic that permits simultaneous estimation of gastric secretion and evacuation have shown that atropine given to patients with pyloric obstruction inhibits gastric emptying more effectively than it inhibits gastric secretion.

I have noted, as many others have, that patients with chronic duodenal ulcer and partial pyloric obstruction often respond favorably to an ulcer regimen that incorporates antispasmodic drugs. These results, therefore, should not be construed as a general plea to abandon the use of anticholinergic agents in the treatment of this condition. Clinical observations, however, also emphasize that atropine and Banthine may aggravate the gastric retention in some patients with pyloric obstruction.[14,15] These findings and the

SUMMARY AND CONCLUSIONS

By means of a barium-radiographic technic the effect of belladonna alkaloids on gastric evacuation was studied in 15 patients with pyloric obstruction complicating chronic peptic ulcer. In 9 patients the drugs produced or increased gastric retention. In 4 of the 9 complete retention was seen at five hours. The results obtained appeared to be due to decreased gastric peristalsis and tone.

In view of these findings and the clinical observations that antispasmodics may aggravate pyloric obstruction in some patients it is suggested that belladonna alkaloids be used cautiously in patients with

benign pyloric obstruction and discontinued if the patients fail to improve.

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TABLE 2 *(Concluded)*.

Drug	Radiographic Observation after Medication					
	Tone & peristalsis immediately after swallow	Barium in stomach at				
		end of 1st hr.	end of 2d hr.	end of 3d hr.	end of 4th hr.	end of 5th hr.
		%	%	%	%	%
Bellafoline (0.5 mg. subcutaneously)	Decreased tone & peristalsis	80	70	30	20	15
Bellafoline (0.5 mg. subcutaneously)	Decreased tone & peristalsis	80	50	20	0	
Bellafoline (0.5 mg. subcutaneously)	Atonic; no peristalsis.	80	50	30	10	0
Bellafoline (0.5 mg. subcutaneously)	Moderate tone; occasional peristalsis.	15	10	0		
Bellafoline (0.5 mg. subcutaneously)	Atonic; normal peristalsis.	50		10	0	
Bellafoline (0.5 mg. subcutaneously)	Normal tone & peristalsis	40	25		15	2
Bellafoline (0.5 mg. subcutaneously)	Decreased tone & peristalsis					5
Bellafoline (0.5 mg. subcutaneously)	Decreased tone; occasional peristalsis.	50		50		25
Bellafoline (0.5 mg. subcutaneously)	Moderate tone & peristalsis					0
Bellafoline (0.5 mg. subcutaneously)	Atonic; no peristalsis.			25		5
Atropine (0.6 mg. subcutaneously)	Normal tone & peristalsis		0			
Atropine (0.6 mg. subcutaneously)	Normal tone & peristalsis	20		0		
Bellafoline (0.5 mg. subcutaneously)	Atonic; occasional peristalsis.	100	75		60	25
Bellafoline (0.5 mg. subcutaneously)	Normal tone & peristalsis		0			
Atropine (0.6 mg. subcutaneously)	Normal tone & peristalsis	80	40	20		2

SPECIAL ARTICLE

MEDICAL EDUCATION IN ISRAEL

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JERUSALEM, ISRAEL

IN 1953 the number of physicians in Israel was 3717, including 700 woman doctors. This number brings the doctor-population ratio in Israel to 1:430, which is one of the highest in the world. Eighty per cent of these physicians work in towns,—about 2400 alone in the three main cities of Jerusalem, Haifa and Tel Aviv,—so that practically 65 per cent of the doctors are serving 45 per cent of the population. More than 30 per cent of these physicians immigrated to Israel after the establishment of the State in 1948, but more than 90 per cent of the total number of Israeli doctors had practiced medicine in their countries of origin before immigration.

The 60 members of the faculty of Hadassah Medical School are graduates of about 50 universities from 16 different countries of Europe, the Americas, Asia and Africa. For instance, each of the 5 teachers in the Department of Anatomy hails from another country—Switzerland, South Africa, Argentina, Italy or Germany. Strange as it may seem the few (150) physicians who graduated from the Medical School during the last two years constitute the strongest group of doctors, with quite a homogeneous medical education.

These few figures may serve to demonstrate the extraordinarily heterogeneous composition of Israel's medical profession, which may be considered a unique phenomenon. Every group of immigrant doctors brought along the knowledge and habits of the respective countries and universities, and it will be many years before "Israeli medicine" can be spoken of in the full sense of the word.

Why, then, despite the high ratio of doctors to population, is there a need for additional medical specialists in this country? The answer lies in the unique social, economic and political developments of the past decades.

Admission of Exiles

In the Declaration of Independence of May 14, 1948, it is explicitly stated that "the State of Israel will be open to the immigration of Jews from all countries of their dispersion." As a result of this policy of the "ingathering of the exiles" the young state, during the first five years of its existence, has seen immigration on an unprecedented scale. The number of immigrants entering Israel during that period exceeded by 200,000 that of those who came to the country during the previous thirty years. The Jewish population, numbering 650,000 in May, 1948, has to date absorbed 750,000 new immigrants (35 per cent from Asia, 15 per cent from North Africa and 49 per cent from Europe).

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Most immigrants come to Israel with no means of their own, and many are in need of special care because of poor health or age, or for other reasons. A considerable number are patients with chronic diseases, whose absorption into the economic life of the country presents special problems because of disability.

This uncontrolled immigration has few precedents in modern history, and its speed and extent greatly affected the medical picture of the country. Of the community of Yemenite Jews, numbering 47,000, who were transferred to Israel by air in the course of one year ("Operation Magic Carpet") 16,000 were in need of hospitalization on arrival. A moderate estimate shows that about 20,000 cases of schistosomiasis have been imported into Israel with immigrants from Yemen and Iraq. Sixty per cent of the immigrants from North Africa are afflicted with trachoma. The large number of tuberculous patients among the new arrivals compelled the State to increase the number of tuberculosis hospital beds from 590 in 1949 to 1986 by the end of 1952.

The transfer of whole communities from Asia and North Africa caused the infant mortality rate to rise from 29:1000 in 1947 to 51:1000 in 1949. As a result of intensified activities in this field the rate dropped to 39:1000 in 1951. The ratio between the occurrence of infant toxicosis among new immigrants and established residents was 17:1.

Finally, the mental and social adjustment of all these heterogeneous groups ("a gap of eight centuries separates the immigrant from Western Europe from his contemporary from the Yemen") constitutes in itself a gigantic medicosocial task entailing the need for closest study and control during the present half of the century.

Apart from the tremendous task involved for the medical profession in Israel in the physical and mental rehabilitation of these immigrant masses, doctors must be ready to face another influx at any time.

National Development

The second factor determining the need for a new generation of physicians is the economic, social and political development of the country and its organic connection with the expansion of existing rural settlements and the establishment of new ones. At present there are about 800 co-operative, collective and other Jewish settlements, with about 500,000 inhabitants in all, whose medical care is in the hands of the 380 physicians employed by Kupath Holim (Sick Fund of the Labour Federation) for this purpose. These settle-

ments (some of them have no more than 100 to 200 inhabitants) are dispersed all over the country, and many, particularly, the newly established ones, are far from towns and main roads, in the Negev Desert and along the frontiers. The organized medical care for their settlers is a grave problem in which the young generation of graduates from the Medical School will have to take an active share.

Health Insurance

About 75 per cent of the population of Israel benefit from health insurance in some form or other, mainly from Kupath Holim, which has a network of hundreds of outpatient clinics and health centers all over the country and maintains 13 (out of the 86) hospitals of the country. More than a third of the doctors in Israel are employed by Kupath Holim. In addition there are a number of smaller health-insurance institutions. Furthermore, there are medical services organized on a community basis, with the encouragement and financial support of the Government, such as maternity and child-welfare clinics, school health services and outpatient departments for the needy. The non-Jewish population, numbering about 185,000, enjoys the same medical services. Arab laborers organized in the Israel Labour Federation and their dependents are members of the Kupath Holim and enjoy full rights, including hospitalization. The remainder are entitled to benefit from governmental and municipal health services under the same conditions as the Jewish population.

This kind of "socialized" medicine, which provides medical care for every citizen of the country (Israel spends more money per capita for medical care than England), necessitates, of course, a vast network of services and the employment of a great number of medical workers.

Age of Physicians

Fifty per cent of the doctors are over fifty years old, among them 600 who have already reached the age of sixty-five and more and who must be replaced during the next few years. Taking into account that the average number of graduates of the Medical School is about 60 each year, it will take ten years just to provide the replacements needed. Moreover, there is a shortage of specialists in certain fields, epecially radiology, anesthesiology, orthopedic and general surgery, ophthalmology and psychiatry. The lack of well trained public-health physicians and of specialists in preventive medicine will certainly make itself felt in the coming years when the reorganization and expansion of the existing health services are undertaken.

Supply of Doctors

Finally, with the destruction of Jewish communities in Europe during World War II, the greatest source of Israel's supply of highly qualified Jewish physicians has dried up. It is one of the foremost tasks of the Medical School to fill the gap thus caused.

How was it possible that, during a period of political and economic difficulties and in the face of seemingly insurmountable obstacles, all these tasks could be tackled and dealt with fairly successfully during the crucial years after the establishment of the State of Israel? Decades of intensive activities of such pioneering institutions as the Hadassah Medical Organization, the Kupath Holim and the Israel Medical Association prepared the field of curative and preventive medicine. With the establishment of the State, the Health Ministry and Army Medical Services joined hands, and finally Malben (the medical organization of the American Joint Distribution Committee in Israel) shouldered part of the burden of providing medical aid for new immigrants through the provision of about 4000 new beds for the disabled and the aged.

Hadassah Medical School

At the outset of the preparatory period leading to the founding of the Hebrew University in Jerusalem the creation of a central medical teaching institution was envisaged, but it took many years of patient planning and building before the dream became reality. The first step toward the establishment of the Medical Faculty had been taken in 1924, when the American Jewish Physicians Committee endowed an institute of microbiology at the Hebrew University.

A plan for a postgraduate school of medicine in conjunction with the Rothschild—Hadassah Hospital in Jerusalem was first put forward in 1927. The negotiations then begun resulted in 1936 in a formal agreement for the establishment of the University—Hadassah Medical Center on Mount Scopus to comprise three units: the Medical School for Postgraduate Study and Research, the Rothschild—Hadassah University Hospital and the Hadassah School of Nursing (subsequently named after the late Henrietta Szold, founder of Hadassah). Under this agreement Hadassah undertook to erect buildings for its hospital (which was given the status of a university institution in 1939) and the School of Nursing on Mount Scopus. The University, for its part, undertook to erect the Ratnoff Building for housing research laboratories, which were then enlarged in accordance with the needs of the Medical Center.

On the completion of the Medical Center in 1939 the Pre-Faculty of Medicine was organized, uniting the medical research laboratories of the University and various clinical departments of Hadassah. This was replaced by the medical faculty in 1949, when the Medical School was opened.

In 1947, everything had been set for the inauguration of the Medical School in the following year with the opening of the first premedical course, with the plan of building up the full curriculum step by step during the next few years. However, during the War of Independence, when the Arab Forces gained control of the road leading to Mount Scopus, the further development of the Medical Center could not be con-

tinued according to plans. Progress was thus slowed down but never definitely interrupted.

The Medical Center was evacuated from its large new quarters and transferred to provisional premises in various buildings in Jewish Jerusalem, none of which were suitable for the needs of a modern medical school. The Hadassah Hospital continued to function and even expanded. It now has a bed capacity of 500, as compared with 350 on Mount Scopus. In addition to its clinical departments, accommodated in four buildings, Hadassah maintains an outpatient department for all branches of medicine, attended by approximately 200,000 patients a year.

In May, 1949, the Medical School was opened, and undergraduate medical teaching was initiated with the opening of the second preclinical year (fourth year of studies). During the following years the curriculum was expanded and since the academic year 1952-53 a full six-year course has been available.

Students, Curriculum and Teaching Methods

Pupils of Israeli high schools (whose curriculums include two years more than those of American high schools) graduate at the age of eighteen. The Medical School provides the premedical training, which is given during the first year and a half of the six-year medical course. After the final examinations at the end of the sixth year of studies students enter the obligatory year of internship, which stands under the faculty's control. At the end of the seventh year, and after presenting his thesis, the graduate obtains the degree of Doctor of Medicine.

At present, about 450 students (17 per cent of them women), from 18 different countries, are enrolled in the seven-year course (including the internship); 84 students graduated from the Medical School in 1952, and 51 in 1953. More than 180 students (the majority of them Israeli students trained abroad) had enrolled in different classes on November 1, 1952, and 70 new students who had enrolled on November 1, 1953 (50 of them in the first premedical year), were selected from among 200 candidates on the basis of a competitive examination and a personal interview.

The economic situation of the students in general is precarious, and most of them are compelled to work. Tuition fees are 100 Israeli pounds a year whereas the student costs the University about 2000 pounds annually. Many of the students receive financial assistance in the form of exemption from tuition fees, scholarships and loans. Close contact is being maintained between the Medical School administration and the Student Association. The textbook lending library for students, recently set up with the aid of contributions received from American physicians, already numbers 2500 volumes, enabling the allocation of a textbook in each of the medical disciplines to every student.

In the teaching program laboratory work, bedside teaching and clinical clerkship are emphasized. Little time is devoted to lectures; the students are taught mainly in small groups and numerous seminars. Instruction is given in Hebrew; a sufficient knowledge of the language is a prerequisite for admission.

The premedical years are allotted to the study of biology, physics and chemistry. In addition courses in psychology, general physiology, genetics, sociology, mathematics and English are given.

The preclinical studies start with anatomy. A special law passed by the Parliament gives the Medical School the right to dissect bodies for teaching purposes. The religious authorities showed full understanding of modern teaching needs and co-operated in the introduction of the law.

So far most of the preclinical subjects have been taught almost independently, but recently efforts have been made for closer integration. With this aim in view a division of physiology, biochemistry and pharmacology has been set up, and the unification of courses in general bacteriology and clinical microbiology has been put into operation.

At the end of this stage of training courses on physical diagnosis, social medicine and introductory courses in medicine and psychiatry are given. A special course in nursing has also been arranged.

The basic medical sciences are represented by 12 departments and 4 research laboratories.

During the first clinical year (the fifth year of studies) the students work in rotation in the hospital wards as clinical clerks; five weeks are devoted exclusively to preventive and social medicine.

The second clinical year is spent mainly in the various outpatient departments and also in rotation, with a month in the psychiatry wards and three weeks of field work in preventive and social medicine. A plan now under consideration would include in the rotation program work in a family health center recently established in a suburb of Jerusalem by the Hadassah Medical Organization. It is hoped that this type of instruction will help medical students attain a more comprehensive approach to medicine.

After completing the six-year medical course and after having passed the final examinations the students are recommended by the Dean for a year of internship in a recognized hospital in the country. Besides the Hadassah—University Hospital in Jerusalem the following institutions have been recognized by the Medical School: the Government hospitals in Tel Hashomer, Haifa, Sarafand and Jaffa, the Beilinson Hospital in Petah Tikvah, the Kaplan Hospital in Rehovoth and the hospital in Affulah (all of Kupath Holim) and the Municipal Hadassah Hospital in Tel Aviv. Furthermore, the Hospital for Nervous Diseases of the Workers' Sick Fund in Jerusalem has been affiliated with the Medical School for undergraduate teaching in psychiatry.

These hospitals also assisted the Medical School in 1950 through the accommodation of two courses of newly immigrated students who had interrupted their studies abroad shortly before conclusion and

were given special complementary instruction before graduating from the Medical School.

Last year a school of dentistry, with 15 freshmen, and a school of pharmacy, with 10 freshmen, were opened in the framework of the Medical School, enlarging the scope and aims of undergraduate medical education of the institution. The opening of the School of Dentistry was made possible by the aid of the Alpha Omega Fraternity in the United States, and the School of Pharmacy owes a debt of gratitude to many pharmaceutical associations abroad for their active assistance in its establishment.

The Medical School derives great benefit from the help of the Medical Advisory Board of the Hebrew University and Hadassah in the United States, consisting of many outstanding medical experts in various medical disciplines.

Teaching Staff

A hundred and eleven members of the academic staff of the Medical School are engaged in teaching. The academic positions are full-time posts, with the exception of those of the heads of clinical departments, who are allowed to conduct a private practice. A number of vacancies for academic teachers exist in the departments of Anatomy, Physiology and Pharmacology. The younger staff members of the Medical School are being sent abroad for further studies and specialization for one or two years. In the last year 25 members of the staff (12 from the basic medical sciences and 13 from the clinical departments) have spent a period of training abroad under fellowships provided by Hadassah, the University and various institutions in the United States and Europe.

Members of the faculty frequently participate in international medical congresses by presenting scientific papers. Close contacts are also maintained with the medical world thanks to the numerous visitors from various countries, who generously offer their knowledge, skill and experience.

Research

Research possibilities are available to the members of the preclinical departments who are free to divide their time and facilities between instruction and scientific investigation.* Also, the staff of the clinical departments in the University Hospital is engaged in research work, and recently special laboratories were established in the Hospital for clinical, cardiovascular and surgical research. In the Medical School there are also a number of laboratories whose main function is the conduct of scientific investigation.

Postgraduate Training

Postgraduate training for physicians is still in the initial stage of planning. The Hadassah Medical Council has recently elaborated a program in which the number of years required for each specialty is laid down.

So far, only refresher courses for physicians have been conducted occasionally. Such courses are arranged by the Hadassah–University Hospital, the Kupath Holim hospitals and the Israel Medical Association. A valuable contribution was made by the Beilinson Hospital through the organization of refresher courses for Kupath Holim doctors.

During the twenty years of its existence the Hadassah–University Hospital has trained a great number of young doctors, some of whom hold leading positions in various medical institutions. However, a great deal is left to be done in this field in the near future. There are plans for a more efficient co-ordination of postgraduate training in the great hospitals of the country. Enough qualified men and well equipped laboratories are now available to assure postgraduate training of a high standard for young doctors from Israel and abroad. The main problem that remains to be solved is the creation of a sufficient number of funds and fellowships to enable the young physicians to benefit from the existing possibilities of training and specialization.

The Medical School takes special interest in this program, being well aware that its teaching and research staff will have to be recruited mainly from the ranks of locally trained men. It believes that young doctors ought to receive at least the initial part of their postgraduate training in the country so as to get acquainted with the physical and psychologic needs of the community they will serve. This, by the way, is also the reason why graduates are not permitted to serve their year of internship abroad (although many favorable offers are put forward), since the school is convinced that they should first of all be integrated into the medical life of the country, understand its specific conditions and requirements and realize the importance of their mission before they can withstand the impact of conditions abroad and the temptation of an easier career.

Development Plans

In June, 1952, the cornerstone was laid for the permanent home of the new Medical Center in Jerusalem.

The master plan for the center, worked out by a well known American architect in consultation with outstanding experts in the field of hospital construction, has just been completed, and building will begin soon. The center will include a complete 430-bed teaching hospital, equipped with modern facilities and labor-saving devices, an undergraduate school for 125 students, clinical and preclinical research laboratories, an outpatient department, a nurses' training school and training facilities for ancillary personnel. It is an ambitious project, which, when completed, will be a source of pride for all who are laboring to make it a true center of healing, teaching and research—the greatest and most modern of the whole Middle East.

*Among the organizations supporting the research activities of the Medical School are the Ford Foundation, the Damon Runyon Cancer Research Fund, the Hematology Research Foundation of Chicago, the Humanitarian Trust in Great Britain, the Medical Branch of the Zionist Federation of South Africa and others. Several contributions in the form of grants and equipment have been obtained from the World Health Organization, the Unitarian Service Committee and various institutions, private leagues and individuals in the United States and Europe.

MEDICAL PROGRESS

ULCERATIVE COLITIS*

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THE medical treatment of ulcerative colitis, like that of many conditions of unknown etiology, has been varied and profuse with results that are unpredictable and often unsatisfactory. Since 1875, when Wilks and Moxon[1] first separated it as an entity from the larger group of specific dysenteries, many theories have been advanced regarding its cause,[2] pathogenesis[3,4] and optimum therapy,[5,6] but no concept has withstood the scrutiny of critical study or the challenging test of time. The absence of a specific etiologic agent has made it necessary to rely on empirical measures for symptomatic control. The resources of skill and patience, fortified at times by the discriminate use of chemotherapy, psychotherapy, antibiotics, steroids and transfusions, are aimed at obtaining remissions, maintaining metabolic and nutritional balance and preventing relapses and invalidism.

GENERAL CONSIDERATIONS

The variability in the natural course of the disease presents an experimental pitfall, and the absence of adequate control studies makes it difficult to evaluate the efficacy of any regimen. The lack of statistical uniformity or sufficient information in different published series concerning the source of the clinical sampling, or the severity and stage of the disease when treatment was instituted, as well as the inadequacy of the follow-up study, casts doubt on their scientific validity. A few examples of the weighting effect of these different factors will suffice. The natural history of idiopathic ulcerative colitis, uncomplicated by therapy, and even the true prevalence of the disease cannot be accurately stated. Mild cases seen in general practice may not be correctly diagnosed in the absence of a sigmoidoscopic examination, and seldom reach the attention of gastroenterologic internists and hospitals, the usual source of published writings on the subject. Thus, the present series in the medical literature may represent only the selected cases — of unknown percentage — whose clinical course has worsened. Even among hospital cases the final outcome may be related to the initial severity; 65 to 80 per cent of patients with disease classified as mild at the onset improved, whereas 70 per cent who were severely ill became worse.[7] The importance of indicating the duration of the colitis at the time treatment is first instituted is strongly suggested by studies on a group of patients not previously treated in any hospital whose disease was less than two years old.[8] Twenty-two per cent of such patients died within a year of this first attack — as opposed to the usual figure of 5 to 10 per cent in large, unselected series. Thus, the mortality is highest in the first two years after the original attack. Any study that fails to distinguish between new and old cases does not convey an accurate estimate of the prognosis.

The significance of the initial attack in establishing a prognostic clue is supported by the x-ray findings of involvement of the entire colon in more than a third of the patients whose symptoms were less than a year old.[9] As a corollary finding, there was no progression of the disease beyond the extent of the damage incurred during the first attack in two thirds of the patients.

The value of any specific method of therapy must be assessed in the light of frequent observations that the prognosis for the individual attack is satisfactory in 60 to 85 per cent of cases regardless of which of the usual medical measures is employed.[10,11] When viewed on the basis of long-term results, however, no method of management has proved uniformly successful.[12] Thus, the longer the interval after any specific regimen, the higher the relapse rate, so that after ten years only 5 to 10 per cent of patients are free of recurrences.[12,13]

In spite of the previously mentioned reservations concerning its true frequency, ulcerative colitis is not a common condition. Its morbidity, however, creates a problem that far exceeds its numerical importance. Although not all recurrent attacks of ulcerative colitis are crippling the ravages of the disease result in varying degrees of incapacity in 40 to 50 per cent of cases, in spite of generally accepted medical measures.[13-15] The seriousness of the problem is graphically demonstrated by the Mayo Clinic study of 2000 cases seen between 1918 and 1937. Twenty years after the first visit to the clinic only 56 per cent of patients were alive, compared to the 83 per cent expected survival rate for the normal population.[16]

The role of chemotherapy, ACTH, cortisone and surgery in any possible modification of this general picture is separately reviewed in detail.

The medical mortality is generally stated to be 5 to 10 per cent.[13,15] However, these figures are compounded in part of attitudes in the past, which considered ileostomy and its management so formidable and undesirable as to warrant persistence in medical

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treatment.[17] Surgery was thus avoided at all costs, with a resulting increase in medical mortality, or delayed to the point where deaths attributed to ileostomy were more properly the result of too prolonged medical management.

Because of their special interest and reputed skill in the management of these cases some clinics and hospitals attract the more seriously and chronically ill as opposed to those seen in a general hospital. Statistics derived from these varying sources naturally influence differences in prognosis and the necessity for surgical intervention.

In reflecting on the numerous unsolved questions in ulcerative colitis one is struck by the many points of similarity to peptic ulcer — for example, in the light of present knowledge, the proper emphasis on control rather than cure, the indications for surgical intervention such as hemorrhage, perforation and intractability, the relation to carcinoma, the susceptibility to stress-producing life situations, the natural tendency to spontaneous remissions and the difficulty of assessing the value of any projected drug or regimen.

Lysozyme

The lysozyme theory is one of the most interesting of the recent concepts of the etiology and pathogenesis of ulcerative colitis, since it combines the infectious and psychogenic factors. A mucolytic and bacteriolytic enzyme first described by Fleming, lysozyme is found in egg white, human tears, gastric juice and other secretions. Its weak, lytic effect against pathogenic organisms soon dispelled the original hopes for its therapeutic efficacy as an antibacterial agent.[18] More recently it has been suggested that excessive amounts of lysozyme, by dissolving and digesting the superficial protective layer of colonic mucus, expose the mucosa to the destructive effect of digestive ferments and intestinal bacteria.[19] The evidence in favor of this hypothesis merits consideration. First of all, superficial ulcerations have been produced in the stomach, small intestine and colon of the dog by feeding of strong solutions of lysozyme.[19] Secondly, lysozyme titer is low in the stools of normal patients and those with colitis during periods of remission.[19] Thirdly, there is a sharp rise during exacerbations of colitis activity in association with feelings of resentment and anxiety and a decrease from the previous high level in response to reassurance or amelioration of the provoking, stress-producing situations.[20] Fourthly, there is a striking increase of lysozyme not only in the stools but also in the involved mucosa of patients with chronic ulcerative colitis during an acute phase of the disease. Fifthly, improvement in the clinical course of colitis with ACTH or cortisone is reflected in a corresponding, prompt fall in fecal lysozyme.[21,22] Sixthly, low values of lysozyme are found in patients with ulcerative lesions besides colitis, as in carcinoma.[20] And, finally, although use of detergents may result in diminished stool lysozyme titer, the lack of corresponding clinical improvement may be due to the fact that the enzyme within the mucosal cells capable of exerting a mucolytic effect on intracellular mucus has not been inactivated.[21]

However, there are objections to the acceptance of lysozyme as the agent responsible for initiating the local lesions of ulcerative colitis. Mucus derived from the colon of fistulous patients is not susceptible to the lytic or digestive action of lysozyme derived from egg white or human tears.[23] In spite of prolonged inhibition of fecal lysozyme by detergents there is no associated clinical improvement.[21] Furthermore, the high lysozyme titer in stools of patients with colitis is due to the high concentration in granulation tissue and leukocytes of whatever cause, and is not specific for ulcerative colitis.[24,25] Experimental production of ulceration in the animal alimentary tract is inconstant, superficial and transient, and requires the use of lysozyme feeding in concentrations much higher than those encountered clinically.[26,27]

Thus, it cannot be decided on the basis of present evidence whether lysozyme concentration is etiologically related to colitis or simply reflects the presence of an ulcerating process and is an index of activity. Certainly, the therapeutic applications of this theory, utilizing antilysozyme agents, have been disappointing up to the present.

Pathologic Physiology

This section analyzes recent experimental efforts and histologic findings bearing on the pathogenesis of ulcerative colitis.

Pancreatic Ferments

Increased amounts of pancreatic ferments delivered to the colon by a hypermotile gut have been postulated as the initiating factor in facilitating the breakdown of colonic mucosa and one of the reasons for the beneficial effect of a sidetracking ileostomy. Although there is one bit of experimental evidence[28] that bile and pancreatic juice or pancreatic juice alone shunted directly into the colon cause a striking inflammatory reaction with mucosal reaction in the rectum and sigmoid, the weight of evidence seems to invalidate this theory. Pancreatic ferments are not increased in patients with ulcerative colitis, and there is contradictory evidence of the failure of colonic mucosa of dogs to be injured by contact with normal duodenal contents.[29] Moreover, the frequency with which ileostomy alone is inadequate as a therapeutic procedure and has to be followed by colectomy weakens the significance of this concept.

Basement-Membrane Changes

On clinical grounds, because it is frequently complicated by arthritis, glomerulitis and erythema nodosum and responds favorably to ACTH and cortisone, an attempt has been made to consider ulcer-

ative colitis a member of the group of collagen diseases.

Biopsy material obtained during sigmoidoscopic examination of patients with ulcerative colitis reveals absence of the normal ground substance in the basement membrane of epithelial cells, with interposition of a homogeneous metachromatic material between the mucosa and the underlying connective tissue.[5] This fundamental alteration in the basement membrane may lead to epithelial sloughing and bacterial infiltration. Changes in basement membrane and connective tissue generally are characteristic of collagen disease.

However, attempts to confirm these specific findings in colitis, using a slightly different technic, demonstrated no constant basement-membrane changes.[30] In addition specimens from patients with enteritis and diverticulitis exhibited the same changes in the basement membrane as a nonspecific sequel to inflammation and leukocytic invasion.[4]

Parasympathetic Hyperactivity

Hyperactivity of the parasympathetic nervous system has been implicated in the pathogenesis of colitis.[31] Attempts to produce the disease in dogs by the use of Mecholyl and acetyl choline have had equivocal results. In one series of experiments[32] the resulting edema, submucosal hemorrhages and superficial erosions were transient; it was estimated that deep ulcerations might have occurred if the period of administration had been prolonged, and the dosage increased to a lethal range. Other experiments[33] utilized daily and prolonged subcutaneous administration of Mecholyl in a beeswax-mineral-oil mixture. Each injection was soon followed by a bloody diarrhea lasting for two or three hours and culminating in erosions and subacute ulceration of the colon after earlier vascular hyperemia, increased capillary permeability and superficial necrosis of mucous membrane. Increased spasm and contractions in a friable bowel may have aggravated the picture.

Such experimental evidence calls attention to alterations in the vasomotor state of blood vessels as the mechanism for mucosal lesions and ulceration. However, for the present, it leaves too many open links in the chain connecting emotional conflicts, imbalance of the autonomic innervation of the large bowel and ulcerative colitis as seen clinically.

Fecal Filtrates

Bacteria-free filtrates, from patients with ulcerative colitis, administered to monkeys, produced no abnormality in the rectosigmoid.[34] However, when incubated with fixed sections of human skin and bowel, fecal filtrates were found to have a disintegrating effect on human epithelium.[35] This effect, which as yet is specific for stools of patients with colitis, could not be reproduced by various enzymes such as lysozyme, trypsin, chymotrypsin and fibrinolysin. The source of this factor — whether microorganism, digestive enzyme or tissue breakdown has not been established. The clinical significance and application of this finding await further study, though the active substance is subject to chemical inhibition in vitro.

Chemotherapy

The inconstant response of the uncomplicated though active phase of colitis to chemotherapeutic agents has been a disappointing climax to the enthusiasm that greeted their first appearance. The results obtained with sulfonamides and antibiotics as revealed in a large survey[5] were no better than those obtained with other methods not directed primarily at an infectious process. Their greatest range of effectiveness is in the treatment of infectious complications and in preparation for surgery.

Of the many sulfonamide preparations in current use the more absorbable ones, such as sulfadiazine, are at times more effective in the acute, toxic stage though their administration cannot be prolonged.[36] The more slowly absorbable drugs like sulfasuxidine and sulfathalidine can be given in large amounts, remaining in contact with the colonic mucosa, and can usually be given safely over a long period. Whatever beneficial effects derive from these agents cannot always be directly correlated with their inhibiting action on the bacterial flora,[37] which is rarely maintained with persistent use.[38]

Recently, an azo compound of sulfapyridine and salicylic acid previously used in the treatment of rheumatic polyarthritis because of its reputed affinity for connective tissue was introduced from Sweden. Since ulcerative colitis also involves the submucous connective tissue, it was deemed applicable to this condition. The most favorable results are those reported by its original proponents, with improvement in 84 per cent and drug intolerance in only 5 per cent.[39,40] In other series, [41-44] from the United States, only 50 to 65 per cent of patients showed improvement, with toxic symptoms of nausea, vomiting, fever, rash or leukopenia in over 20 per cent.

Whereas some observers[13,36,37,45-47] have reported striking and dramatic improvement with chlortetracycline, chloramphenicol and streptomycin, in general, like the sulfonamides, these agents are not curative. They may help induce a remission during the acute toxic phase and lessen the seriousness of purulent complications, but they can themselves produce a severe enteritis and colitis indistinguishable from the disease being treated.[11,48-50] Their indiscriminate use is thus fraught with the possibility of serious complications.

Gastric and Intestinal Extracts

In determining the value of any new regimen, it is difficult to differentiate its possible specific effect

from that produced by the enthusiasm of the physician and the hope of the patient.

Since 1945 extracts derived from hog intestine, stomach and duodenum have been employed in the treatment of ulcerative colitis.[51-53] Their use is based on the theory that in colitis there is deficient elaboration of a hypothetical antiproteolytic substance in the upper gastrointestinal tract. The protection afforded the normal colon by this fraction is denied the patient with colitis, whose bowel is thus rendered susceptible to the autolytic effect of proteolytic enzymes.

Clinical results have been variable. There was a significant degree of intolerance to the different preparations, militating against their continued use. In the acute, fulminating cases of colitis — the group most urgently in need of effective therapy and in which any new preparation can best be evaluated — the results were not impressive.

Medical Ileostomy and Hyperalimentation

The patient with active disease in his colon soon becomes nutritionally depleted because of dietary restriction, increased metabolic needs and excessive loss of essential materials in diarrheal stools and bloody and purulent exudates.[54-57]

In an attempt to simulate a surgical ileostomy and obviate its necessity a Miller–Abbott tube has been passed to the terminal ileum, with constant suction applied to sidetrack the ileal contents from the inflamed colon.[58] At the same time the nutritional needs were met by oral feeding of an enzymatic casein hydrolysate-dextrimaltose mixture in addition to vitamin and mineral supplements. This was carefully regulated in amount, consistence and concentration, to ensure optimum absorption with minimum discomfort, the unabsorbed fraction of the feedings being removed by suction through the tube. The results, as determined by clinical response and x-ray and sigmoidoscopic appearance, were sufficiently gratifying to warrant using this method in 12 cases. Because of the laborious nature of the technic, which requires painstaking co-operation of the ward personnel, and the difficulty some patients had in tolerating an inlying tube, it was not considered feasible as a routine procedure.

To confirm the subsequent impression that the favorable results noted were primarily due to the improved nutritional status as a consequence of hyperalimentation, the studies were repeated in 14 additional patients without intubation but supplemented by transfusions and attention to the emotional problems.[59] The results were excellent in all. The keynote of this method is improvement in nutrition, utilizing a mixture that has little irritating residue and provides a high-protein, high-calorie content in a readily absorbable form. On occasions this mixture may not be tolerated orally because of its unpalatability and tendency to produce nausea and diarrhea. Medical ileostomy would then be reserved for patients with tenesmus, persistent diarrhea and threatened perforation.

ACTH and Cortisone

It is now four years since the first report appeared describing the results obtained with ACTH and cortisone in ulcerative colitis.[60] During this period the rationale, indications and contraindications for their use have been more clearly defined. Now that the first wave of enthusiasm has somewhat receded, their role can be more accurately assessed.[61-77]

In addition to the fact that these preparations would naturally be employed in a disease for which there was no uniformly successful method of treatment, their use was suggested by several considerations. In the first place there are certain similarities between colitis and other conditions such as arthritis, rheumatic fever and asthma in which ACTH and cortisone have proved effective. Secondly, in ulcerative colitis, there is evidence of dysfunction of the pituitary-adrenocortical mechanism, as suggested by disturbances in the urinary excretions of 17-ketosteroids, and impaired eosinopenic response to epinephrine and insulin.[78,79] Thirdly, these drugs can favorably influence appetite, mood and strength, in all of which the patient with colitis may be seriously deficient. Finally, the corticosteroids have an inhibiting effect on inflammatory tissue reaction, diminishing fibroblastic proliferation and consequently fibrosis and stricture formation.[61,63]

It appears that these drugs are most effective in the acute inflammatory phase, with complicating arthritis and erythema nodosum, in which the systemic response is severe, rather than in the chronic type with irreversible cicatrization beyond the submucosa. In the acute, fulminating case of colitis, when one, in desperation, is forced to consider an ileostomy, use of the adrenal steroids may make surgery unnecessary or convert an emergency procedure into an ileostomy performed under more favorable circumstances.[77] However, it is this very tendency to depress fibroblastic proliferation that has made the drugs in the acute, toxic case appear so dangerous to some[80] for fear of precipitating a perforation in a bowel already resembling "a third degree burn covered by a fecal poultice."[81]

Of the various preparations available, ACTH, in a slow intravenous drip, is most economical and effective during the initial phase of treatment. This may be followed by ACTH in gel form for parenteral use. After a satisfactory remission has been obtained cortisone by mouth may be substituted for maintenance purposes.[64]

Many a failure follows the administration of these preparations in too small a dose for too short a time. Some of the reports purporting to show the advantages of ACTH over cortisone reflect this shortcoming. Average doses initially are prescribed as

follows: as an intravenous drip, 20.0 mg. of ACTH in 500 cc. of dextrose in water daily over an eight-hour period, or ACTH, in gel form, 40 to 80 mg. daily. Cortisone initially may be used orally or parenterally in doses of 300 mg. daily. For maintenance purposes 50 to 100 mg. daily is usually sufficient.[84]

In addition to the complications usually associated with these preparations those of special significance in ulcerative colitis include the fact that the decrease in intracellular potassium, which is a potential hazard in severe colitis, may be aggravated, unless compensated for by increased intake.[82] Also, large, undermined, longitudinal ulcers without significant fibrosis — distinctly different from those seen spontaneously in the absence of ACTH therapy — may develop.[83] The coexistence of peptic ulcer and colitis may be more common than previously suspected, and the use of ACTH and cortisone may initiate a dangerous recurrence of ulcer activity.[84,85]

Relapses are common, especially after a short course of treatment, and may occur at varying intervals after cessation of therapy. Whereas repeated courses may induce further remission such a favorable sequel is by no means inevitable. The favorable response is most evident in the improved sense of well-being, remission of fever, improvement of appetite, weight gain and decrease in number and fluid content of stools. However, the appearance of the bowel on x-ray or sigmoidoscopic examination improves only much later, if at all.

Thus, ACTH and cortisone are powerful drugs, capable of inducing a clinical remission in some cases of ulcerative colitis. This remission may be temporary, or the signs and symptoms kept in a state of suppression by maintenance doses. They are not curative, should not be used indiscriminately because of their inherent danger and are to be considered as adjuncts to and not substitutes for generally accepted methods of treatment.

Pregnancy in Ulcerative Colitis

The problem of pregnancy in ulcerative colitis has been the subject of increasing interest in recent years.[86-92] Not only is the physician called upon for guidance regarding the advisability of pregnancy but also he may have to consider interruption of pregnancy when the colitis becomes aggravated or makes its first appearance after conception. Only one aspect of the situation can be resolved in definite terms: there is no adverse effect of colitis on pregnancy. The frequency of spontaneous abortion is no greater than that reported for normal persons — approximately 10 per cent.

Although published statistics in general show that, when pregnancy occurs during an active stage, the colitis becomes aggravated in about 40 per cent of cases, with a lesser tendency in those conceiving during the quiescent phase, there are no rigid criteria of prognostic value in the individual case, nor is there an adequate explanation for this worsening effect of pregnancy. The behavior of the patient during any one pregnancy is not an invariable guide to subsequent ones.

The patient's attitude toward pregnancy and the subsequent changes in the family relation may represent a crisis capable of provoking a stressful life situation. To the patient, under these circumstances, pregnancy may be inadvisable. If it is undertaken she will require sympathetic and reassuring support and constant medical supervision, in the event that the situation is aggravated and therapeutic abortion becomes necessary.

Colitis appearing for the first time during pregnancy is often of the acute, fulminating type, with a stormy, virulent course that responds poorly to medical treatment and often ends fatally, in spite of a therapeutic abortion.

(To be concluded)

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MEDICAL INTELLIGENCE

DOCTORS AFIELD

Alexander Jenkins Semmes

ROBERT S. O'LEARY

BOSTON

VARIED are the ways in which, through the ages, doctors have turned afield from the practice of medicine. As poets, scholars, philosophers, musicians and warriors they have won enduring fame, and their names have become household words to generations often unaware of their earlier dedication to medicine. Dr. Alexander Jenkins Semmes, who holds a modest place indeed among these greats and near greats, won distinction solely by virtue of the vocation for which he forsook his profession: after nearly a generation of industrious, conscientious and successful medical practice, he was ordained in the Roman Catholic priesthood.

The first fifty years of his life suggest little inclination to forsake the world for the spirit, though his character seems to have been such as to qualify him for either endeavor: "Deeply religious from early training, he is described as having been gentle and courteous and yet forceful, a man of ready sympathy and broad charity, qualities which well fitted him for his dual role of physician and priest."[1] He was by no means a shrinker from the contacts of everyday life—he engaged in medical practice and teaching, contributed to the lay and medical literature and served for four years on active duty as a surgeon in the Confederate Army; moreover, he was an enthusiastic participant in the inchoate efforts of the medical profession to organize itself on a national scale.

Born in 1828, Dr. Semmes was a descendant not only of one of the old Catholic families of Maryland (his original American ancestor was one of the first settlers to receive a grant of land in the colony after its charter was issued in 1636) but also of officers of the Maryland line in the Revolutionary Army.[2] In his generation a cousin, Richard Semmes, served as a secret agent to the Confederate Army, and another cousin, Raphael Semmes, was commander of the *Alabama* and admiral of the Confederacy after a career of successful privateering against Northern shipping. His elder brother, Thomas Jenkins Semmes, was attorney general of Louisiana before the Secession and represented that state in the Confederate Senate.

Dr. Semmes, after an education at Georgetown and Columbia College, District of Columbia, as well as in Paris, joined his brother in New Orleans, where he was appointed resident physician at Charity Hospital and took an active part in the medical life of his day. In 1857 he was chairman of a committee of the American Medical Association appointed to recommend remedies for the shortcomings and evils in the methods of holding coroners' inquests—"by which the lives and liberties of the innocent may be jeopardized, and the ends of justice frustrated."[3] The recommendations, made at the annual meeting of the Association in Nashville in 1857, served as a basis for Semmes's third published work, *Medico-Legal Duties of Coroners* (he had earlier written "Medical Sketches in Paris" and analyzed a celebrated criminal case under the title "Poisoning by Strychnia—the Gardiner Case"). In 1858-59 he was elected secretary of the American Medical Association.

The growing tension between the two sections of the Union soon put an end to any country-wide activities of men such as Dr. Semmes. Like all members of his family he was an ardent supporter of the South and the principles for which it stood. On the outbreak of the Civil War he joined the Louisiana Volunteers, later serving as surgeon of Hay's Louisiana Brigade, Stonewall Jackson's corps and Lee's Army of Northern Virginia. He also held the positions of surgeon-in-charge of the third division of Jackson Military Hospital in Richmond and medical inspector of the Department of Northern Virginia.

Some of his experience as a surgeon in the field is described in a paper that appeared in the *Lancet*[4] in 1864. The British medical press had eagerly taken over the publication of medical dispatches from Confederate sources, much to the annoyance of the medical journals in the North. The complaint voiced in a leading article in the *Lancet* in 1864 — "We regret to see that the Northern medical journals resent our professional feeling of amity with Southern as with Northern brethren of the profession"[5]—was reflected in bitter accusations by medical writers in the Union; the *Boston Medical and Surgical Journal*, for example, closed a correction of the *Lancet's* misleading and exaggerated report of alleged neglect of insane patients by Northern troops in Virginia with the following remarks:

> So much for the veracious *Lancet*. Verily it has reason to thank Heaven that its countrymen are not as other men are![6]

Since the lack of all supplies and facilities was becoming critical in spite of Raphael Semmes's efforts to break the Yankee blockade, most of the Southern medical journals ceased publication, and physicians in the Confederacy had to depend on the medical press in England. It is possible that Raphael Semmes carried his cousin's paper through the blockade, for a note in the *Lancet* a few months after the article appeared mentions that Captain Semmes, of the *Alabama*, had received an injury of the hand during an engagement with a Union warship.[7]

Dr. Semmes moved to Georgia after the war, settling in Savannah, where he practiced medicine and taught at Savannah Medical College as professor of physiology. He married the daughter of the attorney general in President Andrew Jackson's first cabinet and took up a life of active professional and social interests. He continued his literary activities, with *Notes from a Surgical Diary* (1866), *Surgical Notes of the Late War* (1867) and *Revaccination: Its effects and importance* (1868). In addition he presented papers before the Medical Association of Georgia and wrote articles for literary and nonprofessional periodicals.

After the death of his wife he continued his medical endeavors until the age of fifty, when he forsook medicine entirely and was ordained a priest. He performed the duties of a parish priest for a short time, after which he was appointed president and lecturer on English and American history and literature at Pio Nono College, Macon, Georgia, where he remained for five years. He then became chaplain of the school and asylum of the Sisters of St. Joseph's at Sharon, Georgia, with missionary duty throughout the State, until he was incapacitated by a paralytic stroke in 1895.

During the last years of his life he showed no interest in medicine. Dr. Semmes became Father Semmes and gave himself wholly to his religious duties with the same enthusiasm that he had earlier shown for medical practice. In 1898 he died at Hôtel Dieu in New Orleans, nursed during his last months by the Sisters of Charity, who had been in charge of the nursing staff at Charity Hospital when he was resident physician in his youth.

Except for the war years the life of this physician and priest was simple and undramatic, although full of the activities of both the doctor and the cleric. Perhaps the last twenty years were spent in work not so far afield from the first fifty as they might seem at first glance. Devotion to duty and reverence for life, physical and spiritual, are key characteristics of the best in both professions; the transfer of these ideals to the religious field was all the easier for a man who believed in them so firmly. Whatever one's opinion of the medicine he practiced, the flag he served and the priesthood he adopted, his story echoes the sentiment that struck Henry Adams on his progress through the cathedrals and abbeys of France: "What men took for truth stares one everywhere in the eye and begs for sympathy."

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CASE RECORDS
OF THE
MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 40401

PRESENTATION OF CASE

A seventy-seven-year-old man was admitted to the hospital because of pain in the left leg.

Four days before admission, while gardening, he noted the acute onset of pain in the left foot and ankle, which soon became blue and swollen.

Two years previously he was hospitalized elsewhere for twelve days with a "heart attack." Since that time he had had increasing dyspnea and orthopnea, for which he was receiving digitalis. Several months before admission he noted bilateral intermittent claudication. There was a history of rheumatic fever and hypertension.

Physical examination revealed a man who appeared comfortable and was lying flat. The left foot and leg were purple and swollen to the midcalf. Varicose veins on this side were collapsed below the knee and filled only after five minutes of dependency. The leg was cold and without pulsation below the femoral artery. The border of the heart extended to the left anterior axillary line in the sixth intercostal space. The pulmonic second sound was greater than the aortic. The mitral first sound had a snapping quality. A Grade 3 apical systolic murmur and early diastolic rumble were heard, as was a loud basal diastolic murmur in the aortic area. The remainder of the examination was negative.

The temperature was 97.2°F., the pulse 110 and irregular, and the respirations 20. The blood pressure was 180 systolic, 80 diastolic.

The urine was yellow, with a pH of 5.5, and gave a +++ test for albumin. Examination of the blood disclosed a hemoglobin of 15 gm. per 100 cc. and a white-cell count of 21,300. The nonprotein nitrogen was 31 mg., the total protein 7 gm., the fasting blood sugar 96 mg. and the cholesterol 263 mg. per 100 cc. The prothrombin time was 60 per cent of normal. X-ray films of the chest showed minimal congestion of the lungs, with a cardiothoracic ratio of 17.5:29, and a tortuous aorta. A femoral arteriogram was done, and a block was revealed at the bifurcation of the femoral and deep femoral arteries.

The patient was given digitalis, heparin, penicillin and streptomycin. On the second hospital day arteriotomies at the left femoral, popliteal and posterior tibial areas were performed, and a clot was removed from the superficial femoral artery. The results were poor, without return to normal circulation in the leg, and a supracondylar amputation was done on the eighteenth hospital day. The specimen revealed severe arteriosclerosis, with multiple areas of narrowing. The wound appeared to heal well. On the twenty-fifth and twenty-sixth hospital days the temperature spiked to 102.4°F. after which it returned to and remained normal. On the morning of the twenty-seventh day the patient was noted to be jaundiced. That afternoon he received a transfusion of 500 cc. of blood. Jaundice appeared to deepen progressively.

On the thirty-first hospital day, physical examination disclosed a dysarthric, disoriented man, hiccuping intermittently. He was jaundiced, and a confluent erythematous rash was present over the trunk, arms and thighs. There was dullness at the right costal margin. Cardiac findings were unchanged except for absence of the apical diastolic murmur previously heard. The liver and spleen were not felt. The blood pressure was 90 systolic, 40 diastolic; the pulse was 62 and irregular, the respirations were 20, and the temperature was 99°F.

The urine gave a ++ reaction for bile. Examination of the blood revealed a white-cell count of 20,500, with 78 per cent neutrophils and 5 per cent eosinophils. The serum showed no evidence of hemolysis. The bilirubin rose progressively to 24.3 mg. direct and 36.9 mg. indirect per 100 cc. The prothrombin time fluctuated from 20 per cent to 100 per cent under the influence of parenteral administration of vitamin K. The amylase was 4 Russell units, and the serum lipase was 2 cc. (normal, under 2 cc.). The total protein was 5.2 gm. with an albumin-globulin ratio of 1.6, the alkaline phosphatase 8.8 units, the cholesterol 78 mg., the cholesterol esters 18 mg., and the nonprotein nitrogen 120 mg. per 100 cc.; the serum sodium was 137 and 116 milliequiv., the serum potassium 4.8 and 5.7 milliequiv., the chloride 82 milliequiv., and the carbon dioxide 25 milliequiv. per liter. Serum ammonia was normal on one occasion. A Coombs test was negative. An electrocardiogram was interpreted as showing atrial fibrillation with incomplete left-bundle-branch block.

Crysticillin and streptomycin were discontinued and Hykinone was given. The patient was continued on digitoxin and placed on parenteral and dietary therapy but frequently refused meals and remained drowsy, and his condition deteriorated progressively. The stools were noted to be partially acholic, and on the thirty-fifth hospital day the nonprotein nitrogen was 47 mg. per 100 cc. The rash appeared to fade. The liver edge was felt once just below the right costal margin. The breathing became labored, the blood pressure dropped to 70 systolic, 40 diastolic, and the pulse was 120 and totally irregular. For the last two days the maximum temperature was 102°F., and the patient died on the forty-third hospital day.

Differential Diagnosis

Dr. Claude E. Welch*: This man was at the age when we think seriously of various degenerative diseases, either cardiovascular or malignant. The history immediately before and after admission was devoted entirely to cardiovascular problems. There does not seem to be much reason to doubt the diagnosis of acute arterial occlusion. I doubt if any of the material in the subsequent history will help me determine whether the occlusion was thrombotic or embolic. On examination, besides the evidence of gangrene of the leg, the findings in the heart, which are the only ones of interest, I believe are enough to indicate that he probably had old rheumatic heart disease. In addition he had hypertension; at that time the blood pressure was 180 systolic, 80 diastolic. The white-cell count was elevated, but the other tests were not remarkable. The cholesterol level, which was within normal range, and the prothrombin time, which was within 60 per cent of normal, are not of any real significance.

May we see the few x-ray films, although they will not contribute to the diagnosis?

Dr. John F. Gibbons: This chest film taken on the day of the femoral arteriogram shows a moderately enlarged heart, the left ventricle probably being the largest chamber, and an extremely tortuous aorta. The pulmonary vessels are somewhat prominent, but otherwise there is no evidence of congestion or abnormal densities in the lungs. The femoral arteriogram demonstrates that the superficial femoral artery is blocked about where the deep branch begins, and there is practically no dye in the usual branches of the superficial femoral artery in the lower thigh and leg.

Dr. Welch: One might wonder at the temerity of the surgeons in attempting to preserve a leg that was obviously gangrenous, but at present we are interested in trying to work out some technic that may be of avail. It is not surprising that they did not succeed and that amputation was finally necessary. I

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am told nothing about the course at this time, — whether the patient received blood transfusions, — but at least we know that he was subjected to many needle pricks for diagnostic tests, which I shall take into consideration when I discuss the differential diagnosis of the jaundice.

Suddenly, there was a change in the course. The amputation wound was healing and he must have been about ready to leave the hospital when, on the twenty-fifth and twenty-sixth hospital days, the temperature spiked to 102°F. and then reverted to normal. On the twenty-seventh day, two days after the onset of the fever, he was noted to be jaundiced and from then on the course was progressively downhill, with increasing jaundice and finally death. I am unable to say what the erythematous rash means. It may have been caused by the antibiotics — the penicillin or the streptomycin; or it may have had a more dire significance that I cannot fathom. The cardiac findings were unchanged except for fibrillation. The blood pressure, however, had fallen very sharply to 90 systolic, 40 diastolic, suggesting that a profound vascular accident occurred during that period. The pulse was irregular, and there was no elevation of temperature of any importance.

The laboratory examinations are interesting. The bile in the urine, of course, is important. The white-cell count was not out of line for anybody who is ill. It is interesting to know that 5 per cent eosinophils were present. One might reason either that the stress reaction had not been severe in the presence of all this disease or that the rash had been on an allergic basis and produced a rise in eosinophils. The jaundice that developed was extremely deep. The fact that the prothrombin time had fluctuated, from 20 per cent and up to 100 per cent when vitamin K was given parenterally, gives some evidence of fairly normal physiology in the liver cells that were working. That is not the change that we should expect if the patient had had severe parenchymatous liver disease. The amylase and, I am told, the serum lipase were within normal limits. The total protein was somewhat low. The alkaline phosphatase was normal, and the cholesterol surprisingly low: 78 mg. per 100 cc. One wonders if that was an error in taking the sample. The cholesterol esters were also low. I do not know how to interpret that if it was not an error in the laboratory, unless there was some remarkable change in the patient's metabolism that at the present moment is not entirely clear. The nonprotein nitrogen had risen to 120 mg. per 100 cc. The sodium was fairly normal at first and then dropped off sharply, and the potassium showed a corresponding rise. The chloride was low, and the carbon dioxide was normal. The electrolyte imbalance toward the terminal phase, therefore, was severe. One notes a marked fall in the total osmolarity; the total base was about 120 so that he obviously was very sick from that point of view. The serum ammonia was taken because some of the patients who have had a severe liver disease have had ammonia intoxication. The electrocardiogram gave further evidence of cardiac damage.

I am sure that I am not expected to give a profound dissertation on the cardiac findings. I think we can dismiss them by saying that this man probably had old rheumatic heart disease involving both mitral and aortic valves and extensive arteriosclerosis. I shall therefore pass on to the cause of the jaundice, which is the real problem.

This man was first jaundiced on the twenty-seventh day and died on the forty-third day — in other words, sixteen days from the onset of the disease to death, which is a very rapid course for a patient with jaundice. What causes of jaundice should I consider? Could a gallstone have produced the trouble? If this had been a gallstone, operation should have been done to save him. Several things make me doubt the diagnosis of stone in the common duct. The fatal illness began with a temperature of 102°F. for two days. If it had been due to a stone in the common duct, one would say that the attack started with cholangitis, that jaundice developed when the stone jammed in the ampulla of Vater. If he had cholangitis at the beginning, that impaction should have made the cholangitis much worse, and the course should have been one of progressive chills and fever until death. It was not; he was just deeply jaundiced. With a stone in the common duct usually the bilirubin is not over 15 mg. per 100 cc. direct. Jaundice up to the high level noted here is extremely unusual with a stone. Furthermore, the patient had no pain. Whereas silent stones occur particularly in elderly patients, they are very unusual. There are several reasons, therefore, why a stone is not a very attractive diagnosis.

Could this man have had a tumor that produced extrahepatic block? One or two of the liver-function tests that I should like to know about are missing. Perhaps they were not done. The cephalin flocculation and thymol turbidity would be of considerable interest. There was evidence, however, that the obstruction was not complete since there was a little bile in the stools from time to time. If this had been due to tumor, I should have expected a normal cephalin flocculation and normal thymol turbidity.

DR. RICHARD B. COHEN: The cephalin flocculation was ++ in twenty-four and forty-eight hours.

DR. WELCH: That is very unusual for a patient suffering from tumor. Furthermore, the course is unusual. A patient should not die that rapidly from carcinoma; the liver should have enlarged progressively, or the gall bladder should have been palpable and so forth. The findings do not fit the diagnosis of tumor.

Some parenchymatous liver disease is more likely. Among the ones that I ought to consider is homologous serum hepatitis, which could follow a trans-

fusion. It was early for homologous serum hepatitis to develop. The jaundice appeared approximately twenty-eight days after admission to the hospital. That is a possible diagnosis, particularly in view of the high cephalin flocculation that was noted at the time of death.

I might mention the possibility of acute yellow atrophy. I do not know much about it, but it is so rare that I shall not consider it.

Another condition to consider is a severe vascular lesion involving the liver. It is interesting that when the jaundice appeared the patient seemed to go into collapse and the blood pressure dropped to 90 systolic, 40 diastolic. That is not common with a stone in the duct or with tumor and in my experience is not common with ordinary hepatitis. He was practically in shock at the same time that he became jaundiced. That makes one wonder whether a vascular condition could have produced the jaundice. If some vascular disease involved the liver, what was it? Could it have been a primary thrombosis of the hepatic artery? That is a disease about which very little is known. Could an embolus have involved most of the hepatic artery? The nearest thing to that that we see on the Surgical Service is an interference with the hepatic circulation by ligature of the hepatic artery, which, of course, is rare. Under such circumstances there is a triad of rather severe shock, jaundice and usually pain, but pain is not necessarily present. We also think that pain has to be present with any type of vascular infarction, but that is not necessarily so. Ligation of the hepatic artery will also produce what has been known as the hepatorenal syndrome, which is a very loose term indicating that the kidney does not function well under these circumstances; this patient's kidneys were not functioning very well, as shown by the high nonprotein nitrogen.

I think that he died of parenchymatous liver disease, that he did not have obstructive jaundice from tumor or stone and that the damage was caused by a vascular lesion with thrombosis rather than by homologous serum hepatitis.

DR. EARLE M. CHAPMAN: Dr. Welch's analysis of the situation was very much like ours. This man was transferred to the Medical Service. When we saw him he was deeply jaundiced and apparently in a terminal state from diffuse liver injury. We searched carefully for a history of previous transfusions or needle pricks that may have been given him — some agent that injured the liver. He had had one transfusion two days before the jaundice was noted on the Surgical Service. We thought that the interval between the transfusion and the jaundice was too short to allow for the development of homologous serum hepatitis. We believed that he had in some way taken into his body some agent toxic to the liver, and yet we could not discover what the agent was. Various cultural methods were used and I think up to now have revealed no growth. The treatment was supportive, with intravenous feedings continuously.

I raised the question whether the antibiotics might have provoked liver damage of this degree. No one seemed to think so. The patient received antibiotics on the Surgical Service and continued to receive them on our service. In conclusion we thought that there was an acute destructive hepatic lesion, and we were in doubt about its cause.

DR. WELCH: Did the rash mean anything to you?

DR. CHAPMAN: The rash further supported our idea; it looked like dermatitis medicamentosa. It could have been due to medication — to barbiturates. Dr. Cohn saw him.

DR. ZANVIL COHN: The two diagnoses that we entertained were thrombosis of the hepatic artery and infectious hepatitis rather than homologous serum hepatitis. We believed he had hepatitis, not coincident to his entry to the hospital but previously. He was in hepatic failure, and his condition was rapidly deteriorating.

DR. FLETCHER H. COLBY: Dr. Chapman, should you care to say whether this fits into acute yellow atrophy, and if not why not?

DR. CHAPMAN: Yes; I think this picture fitted what clinicians used to call "acute yellow atrophy of the liver." Certainly, its intensity and rapid course fit that clinical pattern.

CLINICAL DIAGNOSES

Infectious hepatitis.
Arteriosclerotic heart disease.

DR. CLAUDE E. WELCH'S DIAGNOSIS

Parenchymatous liver disease, probably due to thrombosis of hepatic artery.

ANATOMICAL DIAGNOSES

Infectious hepatitis.
Cardiac hypertrophy, hypertensive type.
Hydrothorax, bilateral.
Ascites.
Infarcts of lung, kidneys, spleen and brain.

PATHOLOGICAL DISCUSSION

DR. COHEN: At post-mortem examination this man was quite jaundiced. The erythematous rash had faded. There was about 500 cc. of yellow fluid in each pleural cavity and about 1500 cc. of fluid in the peritoneum. A small pulmonary infarct was noted in the right lower lobe, and the heart was very much enlarged in a hypertensive pattern, weighing 710 gm. Interestingly enough, the valves were perfectly normal. There was no evidence of rheumatic heart disease, either recent or old. The aorta was extensively atherosclerotic, and 3 cm. above the celiac axis there was a large thrombus, which we believe was the source of the emboli that produced infarcts of the kidneys and spleen and a bile-stained infarction

of the right frontal lobe of the brain. This is an unusual site for a source of emboli in the absence of an aneurysm.

The lesion of interest was in the liver. The liver weighed 1500 gm., which is normal. Scattered throughout was a mottled reddish-brown discoloration that stood out prominently against a lighter tan background. The liver was softer than normal and bulged under the capsule. Histologic examination showed extensive areas of necrosis in which all the cells were replaced by collapsed congested sinusoids. Portal spaces were preserved, but no definite zonal pattern of necrosis was adhered to. There was proliferation of the small bile ducts, with an infiltration of mononuclear cells in the portal spaces. There was evidence of regeneration in the remaining liver cells, but this was not marked. A careful search of the vascular tree, both venous and arterial, revealed no evidence of occlusion or disease.

This histologic picture is compatible with a viral hepatitis in an acute necrotic phase. The necrosis was the type seen in acute yellow atrophy; however, the term in cases of this sort is a misnomer since the changes are due to necrosis rather than to actual atrophy.

The kidney showed a severe bile nephrosis, with extensive bile-stained casts plugging the tubules and degeneration of the epithelial cells lining the tubules.

DR. WELCH: What do you think started this process?

DR. COHEN: I think that the most likely diagnosis is hepatitis of viral origin. To distinguish between homologous serum jaundice and infectious hepatitis histologically is not possible.

A STUDENT: Was the involvement of the liver parenchyma diffuse or patchy?

DR. COHEN: The involvement was more severe in some areas than in others, but the entire liver appeared to be involved.

DR. CHAPMAN: Do you not think that the word "virus" here is a vague use of the word?

DR. COHEN: Perhaps, since there is no proof of its presence in terms of isolation of a virus.

DR. CHAPMAN: One might just as well say that this man had a toxic agent, a chemical agent or a shock mechanism that had affected the liver as well as a virus.

DR. COHEN: I think that is true in many cases of liver necrosis in which a virus is suspected as the basis on clinical and histologic grounds but in which the virus is not isolated. Features of the histology in this case lead us to suspect a virus and exclude the other factors you mention, but the ultimate proof is dependent on actual isolation of the virus. In the last analysis the virus is itself a toxin with particular biologic properties.

DR. WELCH: Do you think a thrombus above the celiac axis diverted blood from the hepatic artery so that there could have been hepatic damage from diminution of blood flow rather than actual thrombosis?

DR. COHEN: The pattern of the necrosis in the liver was against a vascular origin.

A STUDENT: Can you account for the cephalin flocculation test?

DR. COHEN: I believe that in cases of extensive parenchymal damage the cephalin flocculation would be abnormal in just this way.

DR. LOUIS BAKAY: There was one interesting feature about the cerebral thrombosis that the patient had. The infarction of the frontal lobe, which could not be correlated to any clinical finding, had obviously been present for over a month. Although the remainder of the brain was unstained by bile pigment, as the adult brain always is, the infarct contained a good deal of bile pigment and was greenish yellow. The blood-brain barrier had broken down within the lesion. The choroid plexuses were slightly yellow, since they do not belong to the protected part of the central nervous system, but the rest of the brain was not invaded except for the infarct. This happens only when the jaundice is considerable for a long time. I do not believe it would happen with a jaundice of perhaps only a day or so.

A PHYSICIAN: How do you explain the response to vitamin K?

DR. COHEN: The only explanation that occurs to me is that, in spite of extensive damage, there was sufficient active liver parenchyma left to react.

CASE 40402

PRESENTATION OF CASE

First admission. A fifty-seven-year-old man was admitted to the hospital because of increasing fatigue.

He had had gout for eight years, for which he had taken colchicine. Three months before entry he was switched to phenylbutazone because of the nausea produced by colchicine, and for two months before admission he had noticed severe fatigue. For two days before admission he had refrained from taking the medication, and on the day of admission he noted that the toes on both feet had become sore and tender.

The patient was known to have had hypertension for several years and had been on digitalis and a low-salt, low-cholesterol diet. Six years before entry, at another hospital, the nonprotein nitrogen had been found to be elevated. Two weeks before admission he had a brief episode of pressure in the chest associated with some pain in the left arm. During the three months before admission he had noted abundant sweating. There was no past history of dyspnea, palpitation, paroxysmal nocturnal dyspnea, swelling of the ankles, dysuria or hematuria. Nocturia, twice a night, was present. There was no family history of hypertension, gout or arthritis.

Physical examination revealed an obese man in no

distress. A small hemorrhage was seen in the right eye along the inferior nasal artery. The lungs were normal. The heart beat was regular, and there was a presystolic gallop rhythm; no murmurs were heard. A sharp, tender liver edge was felt 4 fingerbreadths below the right costal margin. The spleen was not palpable. There was slight swelling of the ankles. Both great toes were tender. The prostate was twice the normal size and of normal consistence.

The temperature was 99°F., the pulse 100, and the respirations 20. The blood pressure was 220 systolic, 130 diastolic.

Urinalysis showed a specific gravity of 1.008, a + + reaction for albumin and a negative reaction for sugar; the sediment contained 10 red cells, a rare white cell and an occasional granular cast per high-power field. No significant amount of residual urine was found after voiding. Cultures of the urine were negative. A phenolsulfonephthalein test showed less than 5 per cent excretion of dye in fifteen minutes and less than 20 per cent in forty-five minutes. Examination of the blood revealed a hemoglobin of 11 gm. per 100 cc. and a white-cell count of 14,100, with 84 per cent neutrophils. The nonprotein nitrogen was 120 mg., the uric acid 8.2 mg., the fasting blood sugar 114 mg., the calcium 10.4 mg., the phosphorus 7.0 mg., and the alkaline phosphatase 6 units per 100 cc.; the sodium was 142 milliequiv., the chloride 108 milliequiv., the potassium 5.7 milliequiv., and the carbon dioxide 25 milliequiv. per liter. A bromsulfalein test showed 3 per cent retention of the dye. A blood Hinton test was negative. A stool specimen was guaiac negative. An electrocardiogram disclosed an abnormal record characteristic of hypertrophy of the left ventricle. Roentgenograms of the chest demonstrated clear lung fields and moderate enlargement of the left ventricle. Plain films of the abdomen showed the liver at the costal margin; the kidneys could not be outlined, and there was no evidence of urinary-tract calcifications.

The patient received digitalis, colchicine, phenylbutazone and a low-calorie diet and was discharged improved after six days.

Second admission (three months later). In the interim he had felt well until five days before entry, when, an hour after retiring, he was awakened by a tight choking feeling in the throat and had to sit up to breathe more easily. These episodes had recurred on subsequent nights and had not been associated with chest pain. For two days before admission he noted increased shortness of breath even at rest. For the month before entry he had found that sleeping with two pillows was necessary. During the two months before admission there had been two or three episodes of vomiting and associated nausea. He had been on a 1500-calorie diet, but his weight had remained constant. He had felt fatigued and had been on a regimen of limited activity. Two or three attacks of mild gout affecting the great toes and arches of the feet had been readily controlled by phenylbutazone therapy (3 or 4 tablets of 200 mg. each).

Physical examination revealed distended, pulsating neck veins in the upright position. A few moist crackles were heard at the left base posteriorly. The remainder of the physical examination was unchanged.

The hemoglobin was 10.7 gm. per 100 cc., and the nonprotein nitrogen 104 mg. per 100 cc. Urinalysis and other chemical determinations were as before.

An electrocardiogram demonstrated no significant change. Roentgenograms of the chest now showed definite pulmonary vascular congestion and a small amount of fluid in the major fissure on the right.

On a restricted salt diet, increased digitalis and Mercuhydrin the patient gradually lost 5 pounds in weight; the lungs cleared, and he improved subjectively. After two 250-cc. transfusions of packed red cells the hemoglobin was 12.6 gm. per 100 cc. He was discharged after two weeks.

Third admission (four months later). On returning home he had been on a 40-gm. protein diet, with no added salt and 1 gitalin tablet daily. Two months before admission some shortness of breath developed, and he gained 5 pounds in weight. With further restriction of the salt intake, Mercuhydrin injections and increased digitalis, he improved quickly and had returned to full activity. For the six weeks before admission he had had episodes of vomiting, and progressively lost strength and a few pounds in weight. He had continued to have periodic attacks of gout, involving the great toes, ankles and knees, which had responded readily on each occasion to 2 to 3 tablets of phenylbutazone.

Physical examination revealed a pale, chronically ill man who appeared somewhat dehydrated. The neck veins were slightly distended; the lungs were clear, and the heart, abdomen and blood pressure were as before.

Examination of the blood showed a hemoglobin of 7.6 gm. per 100 cc. The nonprotein nitrogen was 230 mg. per 100 cc., and the carbon dioxide 17 milliequiv. per liter. A twenty-four-hour urine specimen of 1090 cc. contained 51 milliequiv. per liter of sodium, and an endogenous creatinine test demonstrated a clearance of 4.4 liters per twenty-four hours (serum creatinine of 14.3 mg. and urine creatinine of 0.57 mg. per 100 cc.).

He was treated with intravenous infusions of fluids, sodium lactate, chlorpromazine and blood transfusions. He improved somewhat, but continued to have episodic vomiting. He was discharged after three weeks; before discharge the hemoglobin was 10.0 gm., and the nonprotein nitrogen 205 mg. per 100 cc., and the carbon dioxide 27 milliequiv. per liter.

Final admission (one week later). After discharge he was on a low-protein, low-salt diet, digitalis, sodium citrate, Amphojel, chlorpromazine and phenylbutazone. He continued to be nauseated, vomited at

least once daily, became quite drowsy and restless, and lost strength. There had been only slight shortness of breath and no nocturnal dyspnea or chest pain and no attacks of joint pain. Physical examination was unchanged except that a presystolic and systolic murmur were now heard at the left border of the sternum.

Examination of the blood showed a hemoglobin of 5.4 gm. per 100 cc. The nonprotein nitrogen was 280 mg., and the phosphorus 9.2 mg. per 100 cc.; the potassium was 7.0 milliequiv., and the carbon dioxide 16 milliequiv. per liter. An electrocardiogram demonstrated sagging of the ST segments in Leads 1, 2, aVL, V_5 and V_6; otherwise, the tracing was unchanged.

He received transfusions of packed red cells, sodium citrate and ion-exchange resin. His condition gradually deteriorated, and terminally Cheyne–Stokes respiration, loud and fine moist rales in both lung fields, distended neck veins and pitting edema of the sacrum developed. During the last two weeks the urine output was about 500 cc. a day. He died five weeks after admission.

Differential Diagnosis

Dr. Allan St. J. Dixon*: Are there any x-ray films of the feet?

Dr. C. C. Wang: No.

Dr. David S. Kahn: X-ray films of the feet done at another hospital (or in a physician's office) were reported as normal. There was no soft-tissue swelling.

Dr. Dixon: May I see the other x-ray films?

Dr. Wang: In the film of the chest taken at the time of the first admission the lung fields are clear and the pulmonary vessels appear normal in size, but the heart is somewhat enlarged predominantly in the region of the left ventricle; the aorta is quite tortuous. There is no fluid in the costophrenic angle. The bones appear normal. In the films of the chest taken on the second admission, there is an increase in pulmonary markings, congestion and enlarged hilar shadows, and there is some fluid in both posterior costophrenic angles. The heart is slightly larger than previously. The appearance is consistent with cardiac decompensation. The chest films taken on the last admission show no appreciable change from that of the first examination. The abdominal films reveal nothing unusual except that I cannot trace the kidney outlines well. There are no calculi. The bones appear normal.

Dr. Dixon: On the first reading, this history seemed fairly classic. People with gout do not usually die of it, but they do die with the complications of nephrosclerosis and hypertension. However, it should be pointed out that there is no definite evidence here for the diagnosis of gout. There is only one sign pathognomonic of gout—namely, urate crystals in gouty tophi. There is nothing in the history to suggest that finding. Furthermore, although one serum uric acid determination was elevated to 8.2 mg. per 100 cc., since this was at a time when the patient had marked nitrogen retention, it is not necessarily significant. There was no family history of gout. It would be helpful if there had been a history of alcoholism.

Dr. Kahn: There was no history of alcoholism.

Dr. Dixon: With deference to Garrod,[1] who wrote about this condition a hundred years ago, I ought to ask if this man had been exposed to lead—the so-called "saturnine" gout.

Dr. Kahn: He was a salesman; he had no known exposure to lead.

Dr. Dixon: However, it is difficult to think of an alternative diagnosis to gout. Gout is frequently associated with hypertension and renal involvement. The patient was a middle-aged man who had episodic arthritis affecting the toes, particularly the great toes, that responded to colchicine, and he had renal disease and hypertension. It is remotely possible that he had an episodic type of rheumatoid arthritis, which can occasionally be confused with gout. By definition such episodic arthritis would appear to respond to any treatment that was tried. The renal involvement may have been related to amyloidosis, but that seems unlikely because he did not have a sufficiently severe arthritis to make one think of amyloidosis. I do not believe this was a secondary gout: there was no evidence of blood disease such as polycythemia or leukemia. I think I must accept this on purely clinical grounds as primary nontophaceous gout.

What was the nature of the poor renal function? The prostate was apparently not large enough to cause obstruction, and the plain film of the abdomen did not show any enlargement of the kidney or any radiopaque stone. Admittedly, a urate stone would not be radiopaque; however, the patient had no clinical symptoms to suggest stones, and with the evidence of gradually increasing renal failure over a long period, I shall have to assume that he had bilateral kidney disease, of which probably the most likely is nephrosclerosis involving both tubular and glomerular elements. He had extremely poor tubular and glomerular function. He had casts in the urine, and he was unable to alter the concentration of the urine. I think he had had relatively benign nephrosclerosis for at least six years, with gradually increasing nonprotein nitrogen retention in the blood and other evidence of failure to excrete what he should have been excreting. Nephrosclerosis is associated with gout in about a fifth of the cases that can be definitely diagnosed.[2] Other patients with gout have albuminuria without other evidence of impairment of renal function. Sometimes at autopsy the kidneys contain urate deposits along the course of the tubules and around the glomeruli. Both tophaceous and nontophaceous gout can be complicated by renal disease, with or without urate deposits in the kidneys.

Did this man have a large liver? It was noted

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clinically on the first admission to be 4 fingerbreadths below the right costal margin. In the x-ray film the liver was of normal size, and the bromsulfalein test was normal. Presumably, the enlargement noted clinically was transient and due to congestion, but I suppose that it might have pointed to amyloidosis.

Did he have complications due to phenylbutazone therapy? Those of us who have used this drug know that there is a high percentage of complications of one sort or another. Agranulocytosis without fever is one of the commonest, but aplastic anemia has been reported. A severe anemia certainly developed later. I do not believe that such a complication was present, but I must bear it in mind.

I have already said that patients with gout frequently have hypertension and other evidence of arteriosclerosis. This man had hypertension, and he also had an episode of central chest pain radiating to the left arm. Regardless of whether this was angina or a small myocardial infarction, it was another bit of evidence pointing to arteriosclerosis. He also had a retinal hemorrhage. I do not believe I have to look further for the cause of the hypertension. It is possible that he had a pheochromocytoma. I doubt if any diagnostic tests were done for that.

DR. KAHN: They were not.

DR. DIXON: The hypertension was presumably either primary or secondary to the nephrosclerosis. I do not know how I could distinguish between the two.

Why did the patient become anemic? Was that part of the uremia? He was given Amphojel and alkali therapy toward the end. Is it possible that he had peptic ulcer, which had been bleeding? One stool was negative for blood.

DR. KAHN: A number were tested, and all were guaiac negative.

DR. DIXON: I assume, then, that the Amphojel was given to impede phosphate absorption from the gut and not because he had an ulcer. The phosphorus metabolism was very much deranged, especially toward the end. It would not surprise me if this man, who had renal failure and an elevated serum phosphorus and phosphatase for this length of time, had some generalized hyperplasia of the parathyroid glands.

How can one explain the terminal course? During the four admissions and in the intervals between he had been vacillating between two dangers. One was that of renal failure and uremia with difficulty in conserving base and secreting ammonia, resulting in increased loss of sodium and acidosis. For this danger adequate amounts of base had to be given to replace what had been lost. On the other hand he had hypertension, with classic left-sided hypertensive heart failure and paroxysmal nocturnal cardiac dyspnea, and later congestive cardiac failure, pulsating neck veins, fluid in the lungs and increased body weight. For this danger the usual treatment of congestive heart failure—digitalis, mercurial diuretics and restricted salt intake—had to be given. Thus, his physicians had to steer a course between giving him too much salt and giving him too little. Finally, he was caught gradually between the two impending failures until he had both congestive cardiac failure and uremia and, terminally, hypostatic pneumonia. The therapeutic difficulties at the end are illustrated by the fact that he was receiving sodium (as citrate) at the same time as the sodium (as chloride) was being restricted.

To sum up, I should think that the diagnosis of gout has to be accepted, but I doubt if the synovial membrane at the time of autopsy revealed anything diagnostic. If it showed a few urate crystals, it would be helpful. I believe that he had nephrosclerosis bilaterally, with uremia, and that the kidneys were probably small, red and contracted, that he had hypertension with cardiomegaly and hypertensive heart failure and that he probably had an old cardiac infarct to explain that episode of chest pain radiating to the left arm.

DR. KAHN: Since the history was abstracted we have gained some additional information in that the blood uric acid level was elevated at a time that the nonprotein nitrogen was found to be approximately normal.

A PHYSICIAN: Would you consider glomerulonephritis?

DR. DIXON: I thought of that, but there was no hematuria. It is conceivable also that the patient had some element of nephrosis. He had significant albuminuria from time to time although this may accompany gout.

DR. VICTOR G. BALBONI: Is the finding of red cells in the urine, with positive sodium biurate in the parenchyma of the kidney, in favor of gouty nephritis over nephrosclerosis?

DR. DIXON: I do not think I can answer that question.

DR. MARIAN W. ROPES: I should agree in general with the diagnosis, but I am interested in the coincidence of the rapid onset of the renal and cardiac failure after he was given phenylbutazone, and I have been speculating on the role that the phenylbutazone may have played in affecting renal function. It is true that gout is associated with nephrosclerosis, but the rapid onset of renal failure occurred after this patient had received phenylbutazone. We know that phenylbutazone in patients who have no known renal disease does produce urine abnormalities. I think it is interesting to speculate about how much of the renal failure was due to the underlying nephrosclerosis and how much to phenylbutazone.

DR. KAHN: Before he received the drug he had evidence of renal impairment.

DR. ROPES: He had an elevated nonprotein nitrogen for years, but many patients with gout have it for years and do not go into failure. It is possible that the gastrointestinal symptoms that occurred before he received phenylbutazone were due to renal failure. In any event, I was surprised that phenylbutazone, which is known to have a damaging effect on kidney function, was continued in a patient in progressive renal failure.

DR. BALBONI: What are the changes?

DR. ROPES: Albuminuria occurs and lasts sometimes for months.

DR. EVAN CALKINS: I saw this patient on his first admission. Among other things we considered a pheochromocytoma, because he was sweating, and had hypertension; however, the degree of renal insufficiency made the diagnosis very unlikely.

DR. FREDERIC C. GOETZ: Why did the hemoglobin drop from 10 to 5 gm. in a week if there was neither blood loss nor hemolysis?

DR. DIXON: I assume that the severe anemia was to be expected in a uremia of this degree. A decreased red-cell survival time occurs in chronic renal disease. In that sense a hemolytic process was present.

DR. ROPES: I think that part of the drop was due to a falsely elevated hemoglobin from transfusions. I assumed that the anemia was associated with renal failure.

CLINICAL DIAGNOSES

Chronic nephritis.
Hypertension.
Congestive heart failure.
Gout.

DR. ALLAN ST. J. DIXON'S DIAGNOSES

Gout.
Hypertensive heart failure.
Nephrosclerosis, with uremia and secondary parathyroid hyperplasia.
Cardiac infarct, old.

ANATOMICAL DIAGNOSES

Nephrosclerosis, severe.
Chronic obstructive nephrosis of gout.
(Uremia.)
Cardiac hypertrophy, hypertensive type.
Splenomegaly.
Parathyroid hyperplasia, secondary.
Hyperplastic bone marrow.
Bronchopneumonia.

PATHOLOGICAL DISCUSSION

DR. KAHN: The most interesting findings were in the kidneys, which were contracted and granular, weighing only 150 gm. together—about one third the expected normal weight. The cortex measured between 0.2 and 0.3 cm. in thickness as compared to the normal of 0.8 cm. These seemed such classic, contracted kidneys that at autopsy, from the gross examination, we all believed that the underlying disease was chronic glomerulonephritis. Microscopical sections, however, revealed that the basic process in the kidneys was a severe nephrosclerosis, which had resulted in destruction of almost the entire functioning units and in which every artery and arteriole in the kidney showed involvement. In the medulla precipitation of crystalline material that stained specifically for sodium urate was found; some of this material appeared to be in collecting tubules, and other crystals were surrounded by a mild inflammatory reaction with some giant cells and their location could no longer be definitely defined. Quantitatively, there were not a large number of these deposits, and I do not think they could have played more than a small part in the mechanism of the renal insufficiency. However, the finding does corroborate the diagnosis of gout since it is not usually observed in nephrosclerosis with renal insufficiency, nor was there any apparent reason for secondary gout. We did not find any tophi; we were not allowed to dissect the joints, but externally the great toes showed only some soft-tissue thickening. Dr. Charles L. Short, who followed this patient for a number of years, believed that on clinical grounds this was indubitably a case of gout.

The heart weighed 650 gm., and the left ventricle was hypertrophied. There was only mild coronary sclerosis, and no area of old or recent myocardial infarction was found. The spleen weighed 450 gm. but showed no histologic abnormality. The bone marrow was hyperplastic, with evidence of active erythropoiesis; it is interesting that in a clinicopathological conference recently held at the New England Medical Center[3] a patient with gout, nephrosclerosis and severe anemia was found at autopsy to have not only a hyperplastic marrow but also extramyeloid hematopoiesis in the liver and spleen. If the anemia had been in any way related to the phenylbutazone therapy one would have expected an aplastic anemia so I think we can eliminate any relation between this therapy and the anemia. Other findings of interest were secondary hyperplasia of the parathyroid glands and renal osteitis fibrosa of a mild degree. There was also a terminal bronchopneumonia.

Hench[4] stated that as far as the life of the patient with gout is concerned the renal complications surpass those of the joints in importance. It is agreed that the uric acid deposition in the kidneys plays at the most only a small part in the renal impairment as a rule and that most often the process in the kidney is severe nephrosclerosis. Why there is this increased prevalence in gout of arteriosclerosis, especially in the kidney, and of hypertension is not understood.

DR. ROPES: Some people question whether it does occur in gout more often than in normal persons. Most of us think that it does but have no knowledge of the mechanism.

DR. KAHN: Except for the kidney there was no more arteriosclerosis than would have been expected at this age and possibly less in some organs than would have been predicted for the duration of his hypertension.

DR. ROPES: I believe that nephrosclerosis is much more common with gout.

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NEW VIRAL AGENTS FROM FEBRILE EXANTHEMS

FROM time to time physicians are confronted by outbreaks of febrile illnesses that do not follow the normal patterns of disease with which they are familiar and do not correspond to the ones generally described in textbooks. In the past, illnesses associated with a rash were usually characterized by the nature, distribution and evolution of the lesions, as well as the course of the fever and symptoms. However, it is now recognized that the pathogenesis, possible mode of spread, epidemiologic significance and methods of control of such diseases can be fully understood only if their causative agents are discovered. Although the epidemic nature of most of these conditions has strongly suggested a microbiologic organism as the cause, the known bacteriologic and virologic methods have, until recently, failed to reveal such agents even in such common exanthems as measles, rubella and chicken pox.

Obviously, new methods were needed to solve these problems. The intracellular nature of viral and rickettsial agents has given rise to procedures involving the propagation of rapidly growing and multiplying cells for this purpose. Embryonated hens' eggs have proved most fruitful as a cultural medium for isolating and propagating many such agents, and, more recently, the use of newborn mice has yielded a host of new viruses of the so-called Coxsackie group, some of which have been shown to be the cause of specific syndromes, notably herpangina.[1] The technics of tissue culture, however, had been successful only in maintaining certain viruses after they had been established, but had generally failed to uncover new viral agents, especially from human sources. The use of human tissues, particularly embryonic tissues, as developed by Enders and his co-workers, has greatly increased the scope of these methods by revealing agents with cytopathogenic effects on the growing tissue cells. Also, as noted previously in these columns,[2] cultures of cells from malignant lesions and from adenoid tissue have yielded many cytopathogenic agents, at least one of which has already been shown quite convincingly to be etiologically related to acute respiratory infections.

In his address given at the Passano Award Dinner, Dr. John F. Enders,[3] the recipient of the award, briefly summarized some of the additions to the knowledge of poliomyelitis and other infections that have been made in his laboratory through the application of tissue-culture technics employing human cells. The reference to "other infections" included the isolation, by Dr. Frederick C. Robbins, of a number of hitherto unrecognized viruses from the feces of patients with symptoms of nonparalytic poliomyelitis or transverse myelitis. Also, in the same laboratory, Dr. Thomas H. Weller for the first time suc-

ceeded in propagating the viruses of chicken pox and herpes zoster in cultures of human tissue.

During the late summer of 1951, in and around Boston, there was an outbreak of a mild illness affecting mainly children and characterized by a skin eruption that in some respects resembled but was not identical with that of rubella. The clinical and epidemiologic features of this outbreak were recently described by Neva, Feemster and Gorbach.[4] By cultural methods utilizing human tissues, Neva and Enders[5] were able to isolate and propagate from the feces of several patients a group of viral agents cytopathogenic for the human tissues. Evidence for the development of neutralizing antibodies against the agents was obtained in almost all the patients whose blood specimens were tested. Cross-neutralization tests indicated that the new agents are immunologically closely related and probably represent a homogeneous group of viruses that are etiologically related to this infection.

During the course of this study, Neva and Enders[6] succeeded in isolating another agent, also cytopathogenic in tissue cultures for cells of human origin, from the feces of a two-year-old child with a febrile illness characterized by a skin eruption; neutralizing and complement-fixing antibodies in the convalescent serum reacting with the agent that was demonstrated also developed. The studies indicated that this agent was different from the one isolated from the patients with the epidemic exanthem. The clinical features in the illness of this patient suggested that the disease was roseola infantum.

Dr. Enders, in his address, indicated that the culture of human cells may compensate for the lack of susceptible animals in the isolation and definition of agents responsible for other diseases of man such as infectious hepatitis, serum hepatitis, German measles and epidemic hemorrhagic fever. These recent experiences indicate that this is not idle speculation. One may hope and even anticipate that the solution of some of these and similar problems will be forthcoming in the not too distant future. This expectation has most recently been fulfilled, in part, by Enders and Peebles[7] in their isolation of a cytopathogenic agent from patients with measles and the inhibition of its effect by convalescent-phase serums from such patients.

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MULTIPLE SCLEROSIS FOUNDATION

THE diagnosis of multiple sclerosis implies a prognosis disturbing and discouraging to patient and physician alike: to the former because of his increased awareness of the more difficult phases of the disease in these days of widespread dissemination of health information and to the latter because of the many years of relatively powerless supervision he will be called upon to give in the face of a progressive, chronic and disabling disease (although a minority of patients do unexpectedly well, escaping unscathed from one attack after the other).

In spite of the basic research that has been done in this disease the answer to treatment still seems as remote as in the days of Carswell, Cruveilhier and Charcot. The causes of remissions and exacerbations remain as baffling as ever. The apparently unpredictable spontaneity of the changes in the course of this illness—for better or for worse—gives rise to undue enthusiasm as well as unwarranted gloom regarding treatment in any small series of cases observed for short periods only.

In most general-hospital clinics these patients do not continue to attend over a long enough period. They drift off, unable to compete with patients who have more clearly responsive, acute illnesses for the attentions of the staff, who, consciously or unconsciously, tend to turn them away. For this reason, six years ago, a clinic was established in this area devoted exclusively to the diagnosis, observation and trial treatment, under standardized conditions amenable to statistical analysis, of large numbers of cases of multiple sclerosis over prolonged periods. In six years more than 600 patients have been followed.

Unfortunately, the clinic was forced to close its doors on March 15, 1954, when the National Multiple Sclerosis Society, which had been supporting it financially since its inception, terminated this assistance as a result of a decision to support only basic research and not clinical research. The clinic was referred to the Massachusetts Chapter of the National Multiple Sclerosis Society, which was to assume the responsibility of maintaining clinical projects devoted to the disease in this area. At a meeting of the Medical Advisory Committee of the Massachusetts Chapter it was voted that full financial support be given the clinic. In spite of the strong recommendations of the Medical Advisory Committee that the research and clinical work not be interrupted, however, the lay board of trustees of the Massachusetts Chapter chose to ignore the advice of its medical committee and voted to deny financial assistance to the only clinical facility exclusively devoted to multiple sclerosis in New England: the Multiple Sclerosis Research Clinic at the Boston State Hospital. It immediately became necessary to cancel appointments, dismiss employees and interrupt the various research projects that were under way. The needs of the many patients for medical supervision were completely ignored, and to date

no provision has been made for these patients whose medical care was so abruptly terminated. As a protest against this attitude the Medical Advisory Committee of the chapter resigned in a body.

Since that time a group of men and women aware of the difficulties being encountered by the Clinic have formed an independent organization, the New England Multiple Sclerosis Foundation, Incorporated, devoted to raising sufficient funds to support the activities of the Boston State Hospital Multiple Sclerosis Research Clinic. The new organization is encountering the usual delays in raising the necessary funds to underwrite a full year's work of the clinic. However, it is anticipated that the endeavors in this field will soon be resumed, at least on a limited basis. Just before the clinic was forced to suspend activities important new avenues of research were being opened, and it is to be hoped that these will be followed in the near future.

NEW ENGLAND POSTGRADUATE ASSEMBLY

THE annual New England Postgraduate Assembly, arranged by the Committee on Postgraduate Assembly of the Massachusetts Medical Society under the auspices of the six New England state medical societies, will be held this year on October 25, 26 and 27 at the Hotel Statler in Boston.

In the thirteen years since the Assembly was introduced to the physicians of this area under the leadership of Dr. Leroy Parkins it has developed from a one-day stand to a full three-day course of exercises and has been so modified as to meet the most up-to-date requirements of modern postgraduate medical education. These changes consist largely of the shift from a series of formal lectures to an organized if brief course of instruction with the main emphasis on panels, symposiums, luncheon meetings and the like, which offer a greater degree of flexibility than did the previously standardized procedure. This year two clinicopathological conferences will be held, on the second and third days of the Assembly. To offset these dramatic episodes, that social relaxation so necessary to the burdened medical mind of today will be afforded by a cocktail party on the afternoon of the first day, and the customary jamboree, so successful in previous years, on the evening of the second day.

It is gratifying to note that the attendance at the Assembly has increased regularly during the past three years, and the Committee wishes to emphasize the welcome that is extended particularly to medical students and the resident staffs of hospitals. The microscopic registration fee of $10, although representing a slight increase over previous years, is almost embarrassingly small when one considers the wares that are offered and the meager purchasing power of today's dollar.

Although some lofty minds, wrapped up no doubt in their own thoughts, tend to confuse the Postgraduate Assembly with the Postgraduate Medical Institute, no confusion is really necessary. Both have to do with postgraduate medical education, it is true, and both are conducted under the scholarly aegis of the Massachusetts Medical Society. Otherwise, they are independent activities except insofar as they supplement each other's work.

EXOGENESIS OF CHICLE-CELL TUMOR

AN inquiry from a British correspondent regarding the possible effects on the human frame of what is considered over there as the universal American habit of gum chewing prompted a casual investigation of the scientific literature dealing with this particular fact of life. A vicarious inspection of the files of the *Quarterly Cumulative Index Medicus* for the eleven years 1942 through 1952 disclosed only 19 references to the subject. Others may have been differently indexed, and since the query referred only to the impact of the addiction on human physiology such issues as the sidewalk exanthem referred to in the *Journal* of February 4, 1954, seem irrelevant.

A casual inspection of the references indicates that 10 deal with the use of chewing gum as a vehicle for various therapeutic substances ranging from acetylsalicylic acid to nitrofuran and the sulfonamides, and the others are varied. Of special importance, although not world shaking, is an article suggesting that gum chewing has no effect on caries, gingival inflammation, calculus formation or bite pressure, but does reduce salivary débris by 82 per cent.[1] Another neat bit of investigation indicates that gum chewing may effect slight reduction in gastric acidity for a short period[2]; the possibility that this reduction may result from dilution with saliva is not mentioned. Still another observer found that this relatively fruitless form of mastication causes a slight rise in oral temperature, and warned against the making of false diagnoses as a result.[3]

To learn that gum chewing has no apparent effect on bite pressure is a chastening experience, leading one to question the long-suspected etiology of lantern jaw, at least as it is found in the Americas. True, Dick Tracy has never been seen to open his mouth wide enough for the insertion of a wad of gum; on the other hand, who but his creator can say that Andy Gump is not a chicle addict?

Perhaps mandibular development is not an attribute of the strong, silent gum chewers but pertains rather to those who, like Father William, have used their jaws in the marital luxury of daily debate.

REFERENCES

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2. Smith, C. S., Wikoff, H. L., and Southard, M. E. Effects of gum chewing on gastric acidity in healthy individuals. *Am. J. Digest. Dis.* **13**:245-247, 1946.
3. Searcy, H. B. Chewing gum fever. *J.M.A. Alabama* **13**:266, 1944.

By the annexation of the city of Charlestown to Boston, a dozen or more of the physicians of the former city will probably become members of the Boston Medical Association, and Suffolk District Medical Society.

Boston M. & S. J., *Oct. 11, 1854*

MASSACHUSETTS MEDICAL SOCIETY

FRANCIS TENNERY HUNTER

1896-1954

Francis Tennery Hunter was born in Amherst, Ohio, on October 22, 1896, and died in Chestnut Hill, Massachusetts, on September 7, 1954. A graduate of Harvard College in the class of 1919 he received his master's degree in 1922 and graduated from the Medical School in 1924. During World War I he drove an ambulance with the French Army. He served in the United States Navy in World War II, retiring at its close, after considerable service in the Pacific, with the permanent rank of captain.

In medicine Frank Hunter's activities were happily divided between clinical and laboratory interests; an authority on diseases of the blood he also served for many years as director of the Baker Laboratory of the Massachusetts General Hospital. His mind was always fresh and inquiring; knowledgeable about "ships and seas and sailors," he maintained as a true avocation a concern with books and literature, of which his interest in Egyptology serves as an example. The pleasure he derived from his personal friendships was balanced by his enthusiastic appreciation of ideas.

One of his most useful contributions to medical progress was the study that he made, with Merrill, Trump and Robbins, on "The Protection of Personnel Engaged in Roentgenology and Radiology." This investigation, the results of which were published as a preliminary report in the *Journal* on July 21, 1949, and as a final report by Hunter and Robbins on January 4, 1951, was financed by a fund raised in memory of Hunter's friend, Dr. Robert N. Nye, the late esteemed editor of this *Journal*.

In view of his love for books, and especially rare books, it is natural that Frank Hunter should have had a lasting regard for the Boston Medical Library, of which he was a member of various committees, and a trustee when that board was established in 1937. This interest took a practical and touching form in one of his last wishes: that instead of flowers for his services friends should send contributions to the Library.

The conviction has been expressed that the gifts thus received should form the nucleus of a larger fund with which a permanent memorial to Dr. Hunter may be established within the Library.

BOSTON MEDICAL LIBRARY

CURRENT EXHIBITION

The exhibition now on display in the rotunda features broadside almanacs of the sixteenth century. Three are medical, and 3 were compiled by the German physicians, Antonius Brelock, George Tanstetter and Conradus de Tockler. They date from 1507 to 1572. These broadside almanacs were used by the common people during the fifteenth and sixteenth centuries and were usually worn out. Generally, those surviving have been rescued from book bindings where they were used for lining papers, although a few examples have survived complete. They show various imperfections where they were trimmed and cut at the top or sides to fit the book that was being bound. The Library has an unusual collection for this country, numbering 23 before 1500 and 12 of the sixteenth century.

STACK CONSTRUCTION

The first part of the new addition to the stack building has been completed and is in use for assembling purposes. Likewise, the combined passenger and freight stack elevator is finished and ready for operation. These two projects have been paid for in full from the money raised by the building campaign. Work on the second part has begun and will be completed on or before November 1, when it is expected that funds from those pledged will be available to pay for this final part in full.

After this will begin the task of bringing the periodical sets from storage where they were placed temporarily, the periodicals and books from the two depository libraries and the material from the two warehouse rooms where they have been for some years.

HUNTER MEMORIAL

As a result of the wish of the late Dr. Francis T. Hunter that gifts to the Library should take the place of floral tributes in his memory, a number of his friends are desirous of establishing a permanent memorial to Dr. Hunter as part of the plan for enlarging and modernizing the facilities of the Library. Contributions to this fund will be welcomed and may be sent direct to the Library with this designation.

BOOK REVIEWS

Manic-Depressive Disease: Clinical and psychiatric significance. By John D. Campbell, M.D. 8°, cloth, 403 pp. Philadelphia: J. B. Lippincott Company, 1953. $6.75.

This volume is a fairly direct descendant of the descriptive line of psychiatry established by Kraepelin, of which it is quite a worthy successor. Indeed, there are a great number of direct quotations from that writer and Kretschmer, as well as some interesting references to Burton's *Anatomy of Melancholy*, which make the book all the more enjoyable.

From the outset it is obvious that organicity is to be the keyword, for the author uses the term "disease" whereas more contemporary thought is directed to the term "reaction" or "reaction type," and his thesis is that manic-depressive disease is a dysfunction of the autonomic nervous system. After carefully examining hundreds of cyclothymic subjects, with and without psychosis, he was impressed by the multitude of somatic symptoms that they presented, and on analysis the symptoms were those of autonomic imbalance. Many previous writers have commented on the parallelism of autonomic functions and the emotions and how the forcefulness of the mood leads the patient to adopt certain ideas and reactions; continuing this line of reasoning, Campbell believes that manic-depressive disorder is not a mental disease per se. Hereditary and constitutional factors are always present in the cycloid state, and it requires only a mild series of stresses, at times, to precipitate the psychosis. Among the exogenous stresses are fatigue, loss of sleep, the menses, anxiety, unfavorable home situations and so forth.

The material on which this study is based consisted of about 2000 cases, of which a final group of 522 was selected. The others were eliminated because some other factors such as arteriosclerosis and syphilis were present or because the patients were in the involutional age bracket and had never before presented a manic or depressive episode. Of the patients described, only about 10 per cent were psychotic. Many readers must wonder how the author came across such a large number of cycloid cases, but he anticipates this criticism by pointing out that, in his opinion, many of the cases he discusses tend to be diagnosed by others as psychoneurosis; he thinks that psychotherapy or psychoanalysis is doomed to failure. However, on that account, many of the descriptions do not seem to fit the diagnostic label Campbell gives them, and it is also irritating to read such a statement as "the diagnosis was substantiated when a brother of the patient had a similar episode two years later" even when the diagnosis appeared to be correct. In the fine presentations of the physiology and pharmacology of the autonomic nervous system and of the somatic symptoms of the cycloid patients there are some surprising omissions. The author was unable to establish many such symptoms in the manic or hypomanic phases, but if the autonomic nervous system were truly the seat of the disorder one would anticipate "contrary-symptoms" to those seen in the depressive states. Also, relatively little space is devoted to the erotic subdivision of the autonomic nervous system, and in this connection one looks in vain for the name of Kempf although there are many references.

Bellak, whose name is also omitted from the index, has said, "The treatment of manic-depressive psychosis is, of course, manifold and is often related to an investigator's bias as to etiology." More often, possibly, treatment is based on a clinical "hunch." Dr. Campbell takes one back to the days of Weir Mitchell and proposes that the main principle to be adopted in the treatment of mild cases is the obtaining of rest and relaxation. Furthermore, the symptoms are explained to the patient on the basis of dysfunction of the autonomic nervous system. The author states, "It is gratifying to observe how this knowledge aids in the essential step in treatment i.e., achieving relaxation." The "unreasonable conscientiousness of the cycloid" is discussed with the patient—"he must dispossess himself of his old drive for accomplishment and ambition . . . and learn to develop a new respect for laziness." It is a bit incongruous that the drugs that act directly on the sympathetic and parasympathetic nervous systems are not mentioned in the author's approach to therapy, but he has found that the intravenous mixture of thiamine and nicotinamide is "most helpful in the treatment of these nervously exhausted individuals." In the psychotic states electroconvulsive therapy is the treatment of choice since it acts through the autonomic nervous system and restores the balance.

In summary, this book is like the curate's egg — good and bad in parts. The descriptive chapters are excellent, as are those on the social consequences of the disorder and on cases in childhood and adolescence. The main thesis is very vulnerable as here presented, for the impression is too readily gained that it is only the manic-depressive patient who has trouble with the autonomic nervous system.

IAN HAY BROWN, M.D.

The Relationship Between Psychology and Science. By William Taylor. 12°, cloth, 244 pp. New York: Grune and Stratton, 1953. $2.75.

This learned volume plumbs deep into the oceans of theory about the body and the mind. It is a highly intellectual book, of special interest to psychiatrists and physicians interested in mind-body problems. The author has given much time to the preparation of this book. It is especially rich in its handling of theoretical material, and, although the words are not included in the title, it also deals with philosophy and mathematics. Not light reading, but stimulating, it is charmingly dedicated "To Elsie, for her grace, beauty—and coffee." I imagine many cups of that rich brown liquid were consumed in the production of this volume.

MERRILL MOORE, M.D.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Manual of Clinical Mycology. By Norman F. Conant, Ph.D., professor of mycology and associate professor of bacteriology, Duke University School of Medicine; David Tillerson Smith, M.D., professor of bacteriology and associate professor of medicine, Duke University School of Medicine; Roger Denio Baker, M.D., chief, Laboratory Service, Veterans Administration Hospital, Durham, North Carolina, and professor of pathology, Duke University School of Medicine; Jasper Lamar Callaway, M.D., professor of dermatology and syphilology, Duke University School of Medicine; and Donald Stover Martin, M.D., chief, Bacteriology Section, Communicable Disease Center, Chamblee, Georgia. Second edition. 8°, cloth, 456 pp., with 202 illustrations. Philadelphia: W. B. Saunders Company, 1954. $6.50.

In this new edition a book first published in 1944 has been revised to include newer information on epidemiology and immunology of the mycoses. Chapters have been added on the fundamentals of mycology, in which the descriptive terms used by mycologists are defined and described, and on the contaminants that may be confused with pathogenic species. The book is the combined work of 5 persons. An appendix is devoted to methods. Lists of references to the latest literature are added to the chapters, and there is a good index.

Wine as Food and Medicine. By Salvatore P. Lucia, M.D., Sc.D., F.A.C.P., professor of medicine, University of California School of Medicine. 8°, cloth, 149 pp. New York: Blakiston Company, 1954. $3.00.

The author discusses wine in all its aspects as a food and remedy. He considers the chemistry, physiology and food value and the use of wine in diseases of the various systems of the body, as well as in acute infectious diseases and diabetes mellitus, as a vehicle for medication and in the treatment of the aged and the convalescent. There is a bibliography of 18 pages arranged by chapters and a good index.

The Annual Survey of Psychoanalysis: A comprehensive survey of current psychoanalytic theory and practice. Edited by John Frosch, M.D., Nathaniel Ross, M.D., Sidney Tarachow, M.D., and Jacob A. Arlow, M.D. Vol. 2, 1951. 8°, cloth, 724 pp. New York: International Universities Press, Incorporated, 1954. $10.00.

The second volume of this serial seeks to present the current literature of value in its field. A chapter on dream studies has been added, and the chapter on training and practice has been omitted because of lack of material. A bibliography of the literature for 1951 is appended to the text, and there is a good index.

NOTICES

ANNOUNCEMENT

Dr. Gordon M. French announces the opening of an office for the practice of cardiology and internal medicine at 1180 Beacon Street, Brookline.

POSTGRADUATE SEMINAR IN PEDIATRIC NEUROLOGY AND PSYCHIATRY

The Commonwealth of Massachusetts, Department of Mental Health, announces the twentieth postgraduate seminar in pediatric neurology and psychiatry, to be held at the Walter E. Fernald State School, Waltham, on Wednesdays, October 13 through December 1, from 7 to 9 p.m. The course is open to the medical profession.

SOUTH END MEDICAL CLUB

The next meeting of the South End Medical Club will be held at the headquarters of the Boston Tuberculosis Association, 554 Columbus Avenue, on October 19, at noon. Dr. John B. Hall, Jr., director, Cook County Health Department, will speak on the subject "Public Relations in the Field of Medicine."

MASSACHUSETTS HEART ASSOCIATION KIDNEY SECTION

The Kidney Section of the Massachusetts Heart Association will present a symposium on pyelonephritis in Morse Auditorium, Museum of Science, Science Park, Boston, on October 25 at 8 p.m. The program is as follows:

Recurrent and Chronic Pyelonephritis in Childhood. Dr. Jack Metcoff.

Pyelonephritis: An evaluation of the problem. Dr. Joseph M. Hayman, Jr.

Some Aspects of the Diagnosis and Treatment of Pyelonephritis. Dr. Edward H. Kass.

Physicians and medical students are invited.

MASSACHUSETTS SCHOOL PHYSICIANS' ASSOCIATION

An afternoon meeting and dinner meeting of the Massachusetts School Physicians' Association will be held at the Framingham High School, Union Avenue and Pearl Street, Framingham, on October 13, starting at 4:30 p.m. The dinner will be held at the Maridor Restaurant, Route 9, Framingham, at 6:30 p.m. Dr. Thomas F. Reilly, chairman, Committee on School Health, Massachusetts Medical Society, will speak on the topic "Recent Trends in School-Health Thinking on the National Level."

ASSOCIATION OF MILITARY SURGEONS OF THE UNITED STATES

The annual convention of the Association of Military Surgeons of the United States will be held at the Hotel Statler, Washington, D. C., from November 29 through December 1.

NATIONAL SOCIETY FOR CRIPPLED CHILDREN AND ADULTS

The national convention of the National Society for Crippled Children and Adults will be held in conjunction with the fourth annual Bay State Rehabilitation Conference at the Hotel Statler, Boston, November 2-6.

MEDICAL TELEVISION SHOWS

The dates of the showing of two medical television programs have been changed as follows: "The Doctor" will be presented on the "Cavalcade of America" on ABC-TV on Tuesday, December 7, and the first program of the "March of Medicine" series will be telecast on NBC-TV on October 31 at 5:30 p.m. (EST).

AMERICAN CANCER SOCIETY

The annual meeting and scientific session of the American Cancer Society will be held at the Hotel Biltmore, New York City, October 18 and 19, starting at 9:30 a.m.

The main subject of the session will be "Cancer of the Uterus: A critical appraisal of the problem," including the following topics: epidemiologic aspects; laboratory studies; prophylaxis; detection of early cancer of the uterus; diagnosis of cancer of the uterine fundus; treatment of uterine cancer; and clinical research in uterine cancer.

AMERICAN GOITER ASSOCIATION VAN METER PRIZE

Two honorable mentions and the Van Meter Prize Award of $300 will be offered by the American Goiter Association for the best essays concerning original work on problems related to the thyroid gland. The award will be presented at the annual meeting of the Association in Oklahoma City, Oklahoma, April 28-30, 1955.

Essays on either clinical or research investigations not exceeding 3000 words, typewritten double spaced in English, should be submitted in duplicate to the secretary, Dr. J. C. McClintock, 149½ Washington Avenue, Albany, New York, by January 15, 1955.

AMERICAN BOARD OF OBSTETRICS AND GYNECOLOGY

The next scheduled examination (Part I), written examination and review of case histories for all candidates will be held in the United States, Canada and military centers outside the continental United States on Friday, February 4, 1955.

The candidate must send 20 case abstracts to the secretary, Dr. Robert L. Faulkner, 2105 Adelbert Road, Cleveland 6, Ohio, as soon as possible after receiving notification of eligibility. Lists of hospital admissions must accompany new applications and requests for reopening.

SOCIETY MEETINGS AND CONFERENCES

OCTOBER, 1954–APRIL, 1955. Postgraduate Medical Institute. Page 451, issue of September 9.

OCTOBER 7–28. Consultation Clinics for Crippled Children in Massachusetts. Page 586, issue of September 30.

OCTOBER 8. Pan-Pacific Surgical Association. Page 1092, issue of June 24.

OCTOBER 8. New England Society of Anesthesiologists. Page 544, issue of September 23.

OCTOBER 8 and 9. Academy of Psychosomatic Medicine. Page 748, issue of April 29.

OCTOBER 11–14. Twenty-Ninth Annual Congress of Anesthetists. Ambassador Hotel, Los Angeles, California.

OCTOBER 11–15. American College of Physicians Course. Page 44, issue of July 1.

OCTOBER 11–DECEMBER 8. Postgraduate Seminar in Psychiatry and Neurology. Page 452, issue of September 9.

OCTOBER 12–14. Paraplegia Conference. Page 588, issue of September 30.

OCTOBER 13. Postgraduate Seminar in Pediatric Neurology and Psychiatry. Notice above.

OCTOBER 13. Massachusetts School Physicians' Association. Notice above.

OCTOBER 14. New York Diabetes Association. Page 544, issue of September 23.

OCTOBER 16–22. American Occupational Therapy Association. Page 1092, issue of June 24.

OCTOBER 18 and 19. American Cancer Society. Notice above.

OCTOBER 18, 1954–JANUARY 17, 1955. Hartford Medical Society. Page 496, issue of September 16.

OCTOBER 18–29. New York Academy of Medicine Graduate Fortnight. Page 44, issue of July 1.

OCTOBER 19. South End Medical Club. Notice above.

OCTOBER 22. National Vitamin Foundation Symposium. Page 410, issue of September 2.

OCTOBER 22 and 23. American Trudeau Society (Eastern Section). Page 544, issue of September 23.

OCTOBER 25. Massachusetts Heart Association Kidney Section. Notice above.

OCTOBER 25–27. New England Postgraduate Assembly. Hotel Statler, Boston. Page v, Advertising Section.

OCTOBER 25–27. National Gastroenterological Association. Page 496, issue of September 16.

OCTOBER 25–30. Course in Care of Atomic Casualties. Page 285, issue of August 12.

OCTOBER 27. New England Obstetrical and Gynecological Society. Annual Meeting. Hotel Somerset, Boston.
OCTOBER 27–29. International Symposium on the Hypophyseal Growth Hormone. Page 1092, issue of June 24.
OCTOBER 29. Massachusetts Public Health Association. Fall Meeting. Blake's Restaurant, Springfield, Massachusetts.
OCTOBER 31–NOVEMBER 4. American Institute of Dental Medicine. Page 968, issue of June 3.
OCTOBER 31. Medical Television Program. March of Medicine. Page 631.
NOVEMBER, 1954–MAY, 1955. Sanitary Engineering Center Training Programs. Page 122, issue of July 15.
NOVEMBER 2–5. Fourth Annual Bay State Rehabilitation Conference. Hotel Statler, Boston.
NOVEMBER 2–6. National Society for Crippled Children and Adults. Page 631.
NOVEMBER 3 and 4. M & R Pediatric Research Conference. Page 496, issue of September 16.
NOVEMBER 3–5. National Society for Crippled Children and Adults. Page 44, issue of July 1.
NOVEMBER 6. Massachusetts Hospital School Symposium. Page 495, issue of September 16.
NOVEMBER 12. Memorial Center for Cancer and Allied Diseases Conference. Page 544, issue of September 23.
NOVEMBER 12 and 13. Inter-Society Cytology Council. Page 968, issue of June 3.
NOVEMBER 15–19. American College of Surgeons. Page 496, issue of September 16.
NOVEMBER 15–26. Laboratory Diagnosis of Tuberculosis Course. Page 246, issue of August 5.
NOVEMBER 17. American Trudeau Society. Page 588, issue of September 30.
NOVEMBER 29–DECEMBER 1. Association of Military Surgeons of the United States. Page 631.
DECEMBER 3, 1954; FEBRUARY 4 and APRIL 1, 1955. New England Society of Anesthesiologists. Page 1054, issue of June 17.
DECEMBER 5. American Academy of Dental Medicine. Page 1092, issue of June 24.
DECEMBER 7. Medical Television Program. The Doctor. (Cavalcade of America.) Page 631.
DECEMBER 8. New England Pediatric Society. Page 968, issue of June 3.
DECEMBER 13–17. Congress of Obstetrics and Gynecology. Page 748, issue of April 29.
JANUARY 3–MAY 9, 1955. Postgraduate Seminar in Psychiatry and Neurology. Page 452, issue of September 9.
JANUARY 10–15. Course in Care of Atomic Casualties. Page 285, issue of August 12.
FEBRUARY 7–9. McIntyre–Saranac Conference. Page 410, issue of September 2.
FEBRUARY 11–25. Pan-American Academy of General Practice. Page 496, issue of September 16.
MARCH 7–12. Course in Care of Atomic Casualties. Page 285, issue of August 12.
MAY 4 and 5. American Psychosomatic Society. Page 286, issue of August 12.
JUNE 21–25. National Association for the Prevention of Tuberculosis. Page 540, issue of March 25.

CALENDAR FOR THE WEEK BEGINNING THURSDAY, OCTOBER 14

THURSDAY, OCTOBER 14
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*9:00–10:00 a.m. Combined Medical-Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.
*9:15 a.m. New York Diabetes Association. Memorial Center for Cancer and Allied Diseases, 444 East 68th Street, New York City.
*9:00–10:00 a.m. Arthritis Grand Rounds. Robert Breck Brigham Hospital.
*10:00–11:00 a.m. Medical Staff Conference. Sherman Auditorium, Beth Israel Hospital.
*10:00–11:00 a.m. Surgical Rounds. 5th floor teaching unit, Beth Israel Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m. Thoracic Conference. Suppurative Diseases of the Lungs and Pleura. Dr. Harrison Black. Main Amphitheater, Peter Bent Brigham Hospital.
*11:00 a.m.–12:00 m. Pediatric Conference. Mount Auburn Hospital, Cambridge.
*11:00 a.m.–12:30 p.m. Hand Clinic (Physical Medicine and Rehabilitation Service). Boston City Hospital.
*12:00 m.–1:00 p.m. Serum Sodium. Dr. Maurice Strauss. Stearns Auditorium, New England Center Hospital.
*4:00–5:00 p.m. Pediatric Seminar. Burnham Memorial Hospital (Burnham 4), Massachusetts General Hospital.
5:00 p.m. Case Presentation and Pathological Discussion Followed by a Subject of Special Presentation. Joslin Auditorium, New England Deaconess Hospital.

FRIDAY, OCTOBER 15
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*9:30–11:30 a.m. Medical and Surgical Grand Rounds. Drs. George W. Thorn and Francis D. Moore. Main Amphitheater, Peter Bent Brigham Hospital.
*10:00 a.m. Tuberculosis Surgical Clinic. South End Health Unit, 57 East Concord Street.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m. Cesarean-Section Meeting. Dr. T. Canter. St. Margaret's Hospital, Dorchester.
*11:00 a.m.–1:00 p.m. Medical Grand Rounds. Dr. Proger and Staff. Stearns Auditorium, New England Center Hospital.
*1:30 p.m. Fertility and Endocrine Clinic. Free Hospital for Women, Brookline.
*1:30 p.m. Tumor Clinic. Mount Auburn Hospital, Cambridge.
*4:00–5:00 p.m. Child Psychiatry. Burnham Memorial Hospital (Burnham 4), Massachusetts General Hospital.
*4:00–10:00 p.m. Alcoholism Clinic. By appointment. Washingtonian Hospital, 41 Waltham Street.

SATURDAY, OCTOBER 16
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Anesthesia Conference. Dr. Etsten. Pratt Lecture Hall, Joseph H. Pratt Diagnostic Hospital.
*8:30–10:00 a.m. Orthopedic Staff Conference. Boston City Hospital.
*9:00–10:30 a.m. Surgical Grand Rounds. Dr. Child and Staff. Stearns Auditorium, New England Center Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–12:00 m. Hematology Clinic. Dr. William Dameshek. Pratt Lecture Hall, Joseph H. Pratt Diagnostic Hospital.

MONDAY, OCTOBER 18
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Medical and Surgical Clinic on Diabetic Problems. New England Deaconess Hospital.
*8:30–9:30 a.m. Clinic by entire Surgical Staff and Anesthesia Staff. Cheever Amphitheater, Dowling Building, Boston City Hospital.
9:30 a.m. American Cancer Society. Annual Meeting and Scientific Session. Hotel Biltmore, New York City.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*12:00 m.–1:00 p.m. Clinicopathological Conference (Boston Floating Hospital). Joseph H. Pratt Diagnostic Hospital.
*12:00 m.–1:00 p.m. Pediatric Medical Surgical Rounds. Drs. Baty and Swenson. Pratt Lecture Hall, Joseph H. Pratt Diagnostic Hospital.
*12:15–1:15 p.m. Clinicopathological Conference. Main Amphitheater, Peter Bent Brigham Hospital.
*1:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*4:00 p.m. Clinicopathological Conference. Pathology Conference Room, Beth Israel Hospital.
*5:00–6:30 p.m. Anesthesia Group of the Lahey Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:30 p.m. Hartford Medical Society. Lesions of the Vulva. Dr. John Parks. Hunt Memorial Building, Hartford.

TUESDAY, OCTOBER 19
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*9:00 a.m. Geriatrics Clinic. Peter Bent Brigham Hospital.
9:30 a.m. American Cancer Society. Annual Meeting and Scientific Session. Hotel Biltmore, New York City.
10:30–11:00 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
12:00 m. South End Medical Club. Boston Tuberculosis Association, 554 Columbus Avenue.
*12:00 m. Pediatric Grand Rounds. Cheever Amphitheater, Dowling Building, Boston City Hospital.
*12:00 m.–1:00 p.m. Pediatric Rounds. Burnham Memorial Hospital for Children (Burnham 4), Massachusetts General Hospital.
*12:15–1:15 p.m. X-Ray Conference. Dr. Merrill Sosman. Main Amphitheater, Peter Bent Brigham Hospital.
12:30–1:30 p.m. Medical Journal Club. Joslin Clinic, New England Deaconess Hospital.
*4:00–5:30 p.m. Anesthesia Conference. Dr. Etsten. Stearns Auditorium, New England Center Hospital.
*5:00 p.m. Surgical Journal Review. Mount Auburn Hospital, Cambridge.
*5:00–6:00 p.m. Service Meeting Followed by Clinical Conference (Medical, Surgical, Obstetrical). Faulkner Hospital.
*5:00–6:00 p.m. Pharmacological and Therapeutic Considerations of the Endocrines in Obstetrics. Dr. H. Ohrenberger. St. Margaret's Hospital, Dorchester.

WEDNESDAY, OCTOBER 20
*8:00 a.m. Combined Rounds. Massachusetts General Hospital.
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m. Orthopedic Grand Rounds. Bigelow Amphitheatre, White 3A, Massachusetts General Hospital.
*11:00 a.m. Boston State Hospital Psychiatric Seminar. Reception Building Auditorium, 591 Morton Street, Dorchester.
*12:00 m.–1:00 p.m. Clinicopathological Conference. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*12:00 m.–1:00 p.m. Roentgen Diagnostic Conference. 5th floor teaching unit, Beth Israel Hospital.
*12:30 p.m. Weekly Pathological Meeting. Joslin Auditorium, New England Deaconess Hospital.
*12:30–1:30 p.m. Weekly Staff Review of Autopsies. Dr. William A. Meissner. Joslin Auditorium, New England Deaconess Hospital.
*1:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*1:00 p.m. Massachusetts General Hospital Hand Clinic. Out-Patient Department.
*2:00 p.m. Rectal Clinic. Peter Bent Brigham Hospital.
*2:00–3:00 p.m. Pediatric Conference for Practitioners. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*4:00–5:30 p.m. Fracture Lecture. Boston City Hospital.
*4:00–6:00 p.m. Overholt Thoracic Conference. Joslin Auditorium, New England Deaconess Hospital.
*6:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*7:30–9:30 p.m. Lahey Clinic Lecture. Joslin Auditorium, New England Deaconess Hospital.

*Open to the medical profession.